We thank Prof. Lip et al. for their comments, which focused on the reproducibility of methods used for the assessment of endothelial function. It has been shown in our paper that flow mediated dilatation (FMD) has considerably worse reproducibility than peak blood flow (PBF). This observation is in contradiction to the widespread opinion that FMD is generally a reproducible technique, suitable even for an individual risk assessment [1]. Poor reproducibility of FMD observed in our study was not due to high intra- and interobserver variability—only one observer saw the video-records and the intraobserver bias expressed as the coefficient of variation of the diameter calculation was low (0.87%). Thus we concluded that FMD has high spontaneous intra-individual variability. This fact should be taken into account if similar studies are designed in future. This conclusion is further supported by the fact that normal values of FMD in healthy subjects differ largely among published trials (5.2% in our study, Celermajer et al. [2] reported 10.0% and Kosch et al. [3] even 18.2%), while the values of PBF are relatively comparable [2,3].

Our trial was not primarily designed for the assessment of endothelial function by measurement of plasma levels of cytoadhesive molecules. However, we performed a post hoc analysis of frozen plasma samples to detect levels of von Willebrand factor (vWF) by ELISA (Asserachrom® vWF, Diagnostica Stago, France) of part of the studied subjects. The plasma samples were available from 17 subjects: in all of them at baseline and after fenofibrate and in 16 of them after atorvastatin. All subjects in this subgroup were non-smoking and otherwise healthy males with untreated combined hyperlipidaemia, aged 47.5±9.0 years (mean±S.D.), with a body mass index of 28.3±3.0 kg/m², a systolic blood pressure of 127±12 mmHg, a diastolic blood pressure of 84±7 mmHg, total cholesterol of 7.4±1.0 mmol/l and triglyceridaemia of 6.2±4.8 mmol/l at baseline. After the initial examination, the participants were randomised into two groups. Group I (N=8) received 200 mg of micronised fenofibrate once daily for 10 weeks followed by 10 mg of atorvastatin once daily for the next 10 weeks. Group II (N=9) received the same drugs but in the opposite way. Plasma vWF levels were tested for carry-over and period effects and both were found as non-significant. vWF decreased from 123±19% at baseline to 108±18% after atorvastatin and 104±24% after fenofibrate after fenofibrate. Both effects were statistically significant in cross-over T-statistics (P-value below 0.01), but no significant difference between drugs was observed (P=0.5).

The fact that the changes of vWF reached statistical significance with P-values below 0.01 with only 17 subjects may indirectly show that the reproducibility of this surrogate of endothelial function was higher.

However, we did not tested the reproducibility of vWF measurements. The reports in the literature did not uniformly demonstrated the link between FMD and vWF. For example, Asberg et al. [4] observed a significant improvement of vasomotor endothelial function after atorvastatin in renal transplant recipients, but vWF levels remained unchanged.

We have not found any significant correlation between ultrasound surrogates and vWF: r=-0.18, P=0.5 (N=16) and r=0.47, P=0.19 (N=9) for the correlation of vWF with FMD and PBF, respectively. It should be emphasised, however, that the numbers used for comparison are too low.

We agree that the use of circulating endothelium-derived molecules for an assessment of endotelial physiology seems to be very attractive. However, the ratio of membrane-bound and circulating fractions may substantially vary due to local differences in the rate of extracellular cleavage or the expression of membrane-spanning domains, or may be due to the varying affinity of non-covalent binding at the endothelial membrane. Large differences in the production of endotelim-derived pro-
teins due to local endothelial activation (resulting from an inflammatory response or vessel trauma) may grossly confound systemic levels of endothelial markers. Inherited or acquired abnormalities in protein structure and function might also influence the results.

Finally, we agree with Prof. Lip et al. that the best way of assessing endothelial function is uncertain. However, the possible advantage of vasomotor endothelial function surrogates is that they reflect the net effects of a number of different molecular pathways. Endothelial response may vary under different stimuli and at different parts of the arterial tree. Therefore, it is questionable if any ‘golden standard’ method could exist.

References