experiences and therefore endorse their[1] suggestion to perform multi-centre studies with large number of patients and many time courses to clarify the influence of PVI on the QT-interval. However, we do not agree that only patients off antiarrhythmic drugs should be included but think the inclusion criteria should meet daily practice.

Conflict of interest: none declared.

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Corrected QT interval prolongation after ganglionated plexus ablation: myth or reality?

We read the article with a great interest by Hermans *et al.*[1] published recently in *Europace* Journal entitled 'Pulmonary vein isolation in a real-world population does not influence QTc interval'. In this study, the authors evaluated whether routine pulmonary vein isolation (PVI) induces significant corrected QT interval (QTc) changes. Twelve-lead electrocardiograms were recorded at hospital's admission (T − 1d), 1 day after the PVI-procedure (T + 1d) and at 3 months post-procedure (T + 3m). QTc was calculated using Bazett's, Fridericia's, Framingham's, and Hodges' formulas. There was no statistically significant within-subject difference in QTc Fridericia, QTc Hodges, and QTc Framingham between the recordings. QTc Bazett was significantly prolonged at T + 1d but recovered at T + 3m.

In a recently published study, Chikata *et al.*[2] found that both QTc Fridericia and QTc Bazett are significantly prolonged after PVI. An unintentional modulation of the atrial ganglionated plexuses (GPs) during PVI has been suggested as the possible explanation for this QTc prolongation by the authors. On contrary to this hypothesis, we found significant and durable shortening of QTc after GP ablation in patients with normal QTc range and long QT syndrome.[3,4] A similar QTc shortening effect was confirmed after GP ablation plus PVI in our following work.[5] Shortening of QTc was attributed to the additional sympatholytic effect of GP ablation.

Although earlier reports suggested that only the second parasympathetic neurons exist in the GPs, it is well known that epicardial ganglia contain both efferent parasympathetic and sympathetic neuronal somata and presumably local circuit neurons/interneurons.[3–5] Considering a similar distribution of sympathetic innervation, the achievement of similar and durable denervation on the sympathetic system might be possible after GP ablation. The difference between our experience and prior data may have several explanations. In our current approach, GPs were ablated with bi-atrial ablation approach. Considering the largest number of epicardial ganglia demonstrated intramural clustering between right and left atrial structures, this anatomy may enable bi-atrial endocardial GP ablation to eliminate a significant number of post-ganglionic sympathetic neurons rather than PVI or surgical GP ablation. Whilst it is possible to access substantial part of epicardial ganglia solely through the left atrium, to prevent re-innervation as has been described for the sympathetic fibres after cardiac transplantation, comprehensive coverage may be more likely through bi-atrial ablation. QTc effects of PVI vs. GP ablation plus PVI have not been studied, yet. We therefore cannot conclude how PVI only strategy modulates GPs. We can, however, conclude that GP ablation cannot be associated with QTc prolongation.

Conflict of interest: none declared.

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Corrected QT interval prolongation after ganglionated plexus ablation: myth or reality?—Authors' reply

We thank Prof. Aksu for this valuable and well-balanced discussion on the possible effect of ablation of atrial ganglionated plexuses (GPs) on the QT interval.[1] Their comments are in line with our statement that from our study[2] we neither can conclude that pulmonary vein isolation (PVI) does not modulate GP nor that GP modulation leads to changes in QTc. We can, however, conclude

that, on average, routine PVI does not induce changes in QTc.

Conflict of interest: none declared.

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Beware of the hazards: limitations of the proportional hazards assumption

In a recent issue of the *Journal*, Wu *et al.* presented the outcomes of 'Long-term observation of catheter ablation vs. pharmacotherapy in the management of persistent and long-standing persistent atrial fibrillation (CAPA study)'.[1] The authors reported a study of 648 patients with persistent and longstanding persistent atrial fibrillation (AF) randomized to catheter ablation or pharmacotherapy for rhythm control of AF. After a mean follow-up of 54.2 ± 10.6 months, the primary outcome of stroke, transient ischaemic attack, systemic embolism, major bleeding, or new-onset congestive heart failure occurred less frequently with catheter ablation compared to pharmacotherapy [10.4% vs. 17.4%, hazard ratio (HR) 0.59, 95% confidence interval (CI) 0.48–0.75, $P < 0.001$]. Similarly, recurrent AF/atrial flutter/atrial tachycardia occurred less frequently with catheter ablation compared to pharmacotherapy (HR 0.32, 95% CI 0.16–0.51, $P < 0.001$). The authors are to be congratulated for their impressive work and results.

It is important to recognize the limitations of statistical models when drawing such conclusions.[2] When comparing outcomes and reporting the HRs between groups, log-rank and Cox regression models are typically employed- these are semi-parametric statistical tests that require an underlying assumption of proportional hazards. The assumption presumes that the impact of covariates remains relatively constant and proportional during the follow-up period.[2]

Importantly, the Kaplan–Meier survival curves of both the primary outcome and freedom from AF/atrial flutter/atrial tachycardia suggest that the proportional hazards assumption was violated in both cases. The survival curves demonstrate a complete overlap of outcomes during the first 12–18 months, followed by a marked departure afterwards. The hazard of recurrent events was therefore not proportional over time, but rather was highly dependent on the follow-up period. If applied clinically, informing patients of a 41% reduction in the primary outcome or 68% reduction in recurrent arrhythmias with catheter ablation would be misleading. Rather, the patient should expect no reduction in the primary outcome and atrial arrhythmias during the first 12–18 months, followed by a gradual reduction in the primary outcome and recurrent atrial arrhythmias after that.

Evaluating for proportional hazards can be performed graphically by visual assessment of the survival curves or scatter-plot of Schoenfeld residuals. When the Schoenfeld residuals are plotted over time, a test of trend can be used to evaluate whether proportional hazard assumptions are violated. If violated, one can consider data transformation, or use of a time-varying covariate. Among prior examples in cardiology, the proportional hazards assumption can be violated due to an early or delayed treatment effect, and analyses should be adjusted accordingly.[3–5] Importantly, proportional hazards (or the lack thereof) should have a fundamental clinical basis. In the study by Wu *et al.*, one might question why catheter ablation would be associated with no impact on the primary outcome or atrial arrhythmias during the first 12–18 months, only to have these differences between groups arise later in follow-up. Although the CAPA trial results are undoubtedly significant and have important implications, we must still ensure the appropriate interpretation when discussing these results with our patients.

Conflict of interest: none declared.

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Beware of the hazards: limitations of the proportional hazards assumption—Authors' reply

We thank Cheung *et al.*[1] very much for his thoughtful letter regarding our study (CAPA study).[2] Cheung *et al.* were concerned about the way we interpreted the hazard ratio (HR) of primary outcome or recurrent atrial arrhythmias (AA), and they recommended the visual assessment of the survival curves or scatter-plot of Schoenfeld residuals to be further performed for proportional hazards (PH) evaluation. In fact, in the CAPA study, the HR of primary outcome or recurrent AA was varied over time and changed in magnitude but not in direction, which could be considered as a minor violation of the PH assumption.[3] In our study, the overall HR was calculated by the Cox proportional hazards model, which is widely accepted as being robust to a minor PH assumption violation,[3] could be interpreted as an average HR over time.

Cheung *et al.* also pointed out that the catheter ablation seemed to have no effect on the primary outcome or AA events during the first 12–