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Dementia and death: Separate sides of the atrial fibrillation coin?

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To the Editor,

Recently in the *International Journal of Cardiology*, Marzona et al. reported the association between atrial fibrillation (AF) and risk of dementia in a population-based cohort [1]. Using Cox's cause-specific hazard models, the authors found that atrial fibrillation is significantly associated with risk of dementia in their study population. However, after performing additional (subdistribution hazard) competing risk modelling they conclude that "the association between AF and dementia was no longer statistically significant when death was considered a competing risk". We feel that this conclusion does not do justice to the presented data, because of differences in the interpretation of the cause-specific and subdistribution hazards that are not discussed in the paper.

While competing risk modelling, for example with the subdistribution hazard of Fine and Gray's models [2], can be valuable in *prognostic* studies, they are less appropriate for determining *aetiological* associations in the presence of strong competing risks [3,4]. The fundamental issue with competing risk is that one of the main assumptions for censoring, independence of reasons for censoring, is no longer met. For estimating prognosis, ignoring the fact that death precludes development of an illness overestimates an individual's risk, and one would therefore intuitively want to keep a person in the risk set after occurrence of this competing event. Conversely, in aetiological studies, the primary interest lies in determining the (relative) risk of disease in those who are still at risk of the disease at a certain time-point. These cause-specific hazards are obtained from a Cox model, in which individuals are censored at time of (competing) event. Importantly, independence of reasons for censoring is not required here to obtain valid estimates [3,4]. Of note, neither form of modelling addresses potential underestimation of causal associations, caused by competing events 'masking' the impact of the risk factor on the phenotype of interest.

Practically, this means that the *causal* relationship between AF and dementia is best determined by the cause-specific hazard, using Cox models [3,4]. As such, findings presented by Marzona et al. add to various previous studies to establish a firm association of AF with risk of dementia [5,6], and underline that these associations extend to the elderly population. Although randomised trials assessing effects of treatment of AF on (surrogate markers of) dementia risk are still lacking, Marzona et al. rightly emphasise that current "anticoagulant treatment in patients with AF is still unsatisfactory" in view of available evidence from randomised controlled trials for other disease outcomes. This study in line with others merits emphasis on adherence to current guidelines for AF treatment, if not for prevention of dementia, then for one of life's alternative hazards in which AF plays part.

Conflict of interest

We have no conflicts of interest to report.

References

[1] I. Marzona, M. Baviera, T. Vannini, et al., Risk of dementia and death in patients with atrial fibrillation: a competing risk analysis of a population-based cohort, Int. J. Cardiol. 220 (2016) 440–444.
[2] J.P. Fine, R.J. Gray, A proportional hazards model for the subdistribution of a competing risk, J. Am. Stat. Assoc. 94 (446) (1999) 496–509.
[3] P.K. Andersen, R.B. Geskus, T. De Witte, H. Putter, Competing risks in epidemiology: possibilities and pitfalls, Int. J. Epidemiol. 41 (2012) 861–870.
[4] B. Lau, S.R. Cole, S.J. Gange, Competing risk regression models for epidemiologic data, Am. J. Epidemiol. 170 (2009) 244–256.
[5] C.S. Kwok, Y.K. Loke, R. Hale, et al., Atrial fibrillation and incidence of dementia: a systematic review and meta-analysis, Neurology 76 (2011) 914–922.
[6] R.F. De Bruijn, J. Heeringa, F.J. Wolters, et al., Association between atrial fibrillation and dementia in the general population, JAMA Neurol. 72 (11) (2015) 1288–1294.

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