Title:

Antihypertensive drugs, incident dementia and the competing risk of death

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To the Editor,

In the paper “Antihypertensive Medication Regimen Intensity and Incident Dementia in an Older Population” by Tan et al., the authors reported that, in a prospective observational population-based cohort of 1208 older persons (mean age: 84.1 ±5.6), use of a higher number of antihypertensive drug (AHD) classes was associated with a lower dementia risk during 6 years of follow-up.1 Cox regression was used to estimate hazard ratios (HR) and competing risk of death was adjusted for using the subdistribution hazard method of Fine and Gray.2 The authors concluded that use of multiple AHD classes may convey a reduced dementia risk. This novel finding could have important clinical implications, making replication imperative.

We previously investigated the association between AHD classes and dementia within the preDIVA cohort.3 The preDIVA trial evaluated the effect of nurse-led cardiovascular risk management on incident dementia in community-dwelling older people during 6-8 years. Baseline medication use was based on participant interviews cross-referenced with GP electronic health records. Incident dementia was established by an expert panel based on DSM-IV criteria. Dementia outcome was available for 98.0% and mortality for 99.8% at final follow-up. For the following analyses, we approximated the methods used by Tan et al. using baseline preDIVA data.

In 3278 participants (mean age: 74.4 ±2.5), over 6.3 (±1.5) years of follow-up (20,648 person years), there was no relation between the number of AHD classes used and dementia risk (Table 1), although participants using ≥2 classes had a markedly lower HR compared to those using one. HRs for CCBs and ARBs were comparable to those reported by Tan et al. but substantially higher for diuretics, beta-blockers and ACE inhibitors. Similar to Tan et al., results were unaffected by adjustment for the competing risk of death. Overall, using more AHD classes was associated with a higher cause-specific risk of mortality and dementia/mortality combined.

The difference in findings of the present analyses and those by Tan et al. may originate from the competing risk of death. The subdistribution hazard competing risk model only adjusts the HR to relate to cumulative incidence instead of rate.4 For example, smoking may increase both fatal cancer and dementia HRs, but the increase in death from cancer may be so high as to decrease the actual dementia incidence.5 The subdistribution hazard method attenuates the HR for characteristics that also increase the competing event HR and vice versa.

In the current context, the subdistribution hazard for dementia is perhaps less valuable. Any AHD that reduces dementia incidence by increasing mortality is unlikely to be preferred by clinicians. Dementia-free mortality (the cause-specific HR), defined as the mortality HR with dementia censored as non-event, may be more informative. When equal or below neutral (HR ≤1), it indicates any reduced risk of dementia cannot be ascribed to increased mortality. Our results suggest participants with more AHD classes have significantly higher HRs for mortality (Table 1), potentially explaining the lower HR for dementia.

Considering dementia and mortality as similarly poor outcomes, the combined endpoint dementia/mortality would be most informative. In our analyses, participants using >1 AHD class had an approximately 20% higher risk of death/dementia combined, negating the clinical value of any reduction in dementia risk. The HR for mortality influences the combined HR most since mortality occurred about twice as often as dementia. Mortality in the cohort described by Tan et al. exceeded that in ours (45% vs 15%), possibly magnifying the effect on the dementia HR. Additional analyses regarding the HR for mortality are therefore highly relevant. Only characteristics associated with both a lower dementia and neutral or lower mortality risk can be unequivocally considered to be associated with a lower risk of dementia.

Regarding our results, although polypharmacy itself conveys risks, multiple AHD classes are likely predominantly markers of increased mortality risk rather than causal actors. The number of AHD classes is strongly related to hypertension severity and/or treatment resistance, as doses and the number of AHD are increased step-wise to achieve target blood pressure.6 Such bias may also play a role for specific AHD classes, as some will be more readily prescribed as first-line treatment of hypertension while others (e.g. ARBs and ACE-inhibitors) are generally added later or with particular comorbidity. However, these effects are likely less strong than those for the number of AHD.

In conclusion, although we underline the relevance of the research by Tan et al. on the differential relation between AHD classes and dementia risk, we feel additional information regarding mortality risk is essential to allow for meaningful interpretation of the results.

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|  | **Dementia**  **(n=217/3,278)** | | |  | **Dementia competing risk**  **(n=217/3,278)** | | |  | **Dementia free mortality**  **(n**=**484/3,278)** | | |  | **Dementia and/or mortality**  **(n=703/3,278)** | | | |
| **AHD** | **HR** | **95% CI** | **p** |  | **HR** | **95% CI** | **p** |  | **HR** | **95% CI** | **p** |  | **HR** | **95% CI** | **p** |
| Number (range 0-4) | 0.91 | (0.79 to 1.04) | 0.18 |  | 0.89 | (0.78 to 1.03) | 0.12 |  | 1.14 | (1.05 to 1.24) | 0.002 |  | 1.07 | (1.00 to 1.15) | 0.053 |
| - 0 (n=1479) |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| - 1 (n=766) | 1.11 | (0.79 to 1.56) | 0.54 |  | 1.11 | (0.80 to 1.55) | 0.54 |  | 1.15 | (0.90 to 1.48) | 0.26 |  | 1.14 | (0.93 to 1.39) | 0.20 |
| - ≥2 (n=1033) | 0.83 | (0.58 to 1.19) | 0.32 |  | 0.80 | (0.56 to 1.15) | 0.23 |  | 1.39 | (1.11 to 1.75) | 0.01 |  | 1.20 | (0.99 to 1.46) | 0.06 |
| **AHD classes:** |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Diuretics (n=932) | 1.04 | (0.71 to 1.53) | 0.82 |  | 1.03 | (0.70 to 1.51) | 0.87 |  | 1.18 | (0.91 to 1.52) | 0.21 |  | 1.12 | (0.91 to 1.39) | 0.28 |
| Beta-blockers (n=899) | 1.31 | (0.93 to 1.84) | 0.12 |  | 1.35 | (0.96 to 1.89) | 0.09 |  | 0.85 | (0.67 to 1.07) | 0.16 |  | 0.97 | (0.80 to 1.17) | 0.74 |
| CCB (n=478) | 0.64 | (0.39 to 1.06) | 0.08 |  | 0.66 | (0.40 to 1.09) | 0.10 |  | 0.96 | (0.73 to 1.27) | 0.78 |  | 0.87 | (0.69 to 1.11) | 0.26 |
| ACE inhibitors (n=585) | 1.38 | (0.93 to 2.04) | 0.11 |  | 1.30 | (0.88 to 1.93) | 0.19 |  | 1.23 | (0.97 to 1.57) | 0.09 |  | 1.24 | (1.01 to 1.53) | 0.04 |
| ARB (n=368) | 0.78 | (0.47 to 1.29) | 0.33 |  | 0.78 | (0.47 to 1.30) | 0.34 |  | 0.98 | (0.74 to 1.30) | 0.90 |  | 0.95 | (0.75 to 1.21) | 0.68 |

**Table 1. Hazard ratio’s for dementia and/or mortality according to classes of antihypertensive drugs.** Results of Cox proportional hazard analyses with AHD class use as predictors. Confounders and cut-off values were chosen to best approximate those used by Tan et al. Number: represents number of different AHD classes used. AHD classes: use of specific AHD class, adjusted for concurrent use of any other AHD class (yes/no). Outcomes: Dementia: incident dementia; Dementia competing risk: the sub-distribution hazard of dementia according to they Fine and Gray competing risk model; Dementia free mortality: mortality with dementia cases censored as non-events at the time of dementia (i.e. cause-specific hazard ratio); Dementia and/or mortality: combined endpoint of dementia and mortality, whichever occurred first. Only participants with known dementia (97%) and mortality (99%) status at the end of the study included. All analyses were adjusted for age, sex, apolipoprotein E4 positive/negative/unknown, mini-mental state examination score, total cholesterol >6.22 mmol/litre, blood pressure >140/90, diabetes mellitus, history of vascular disease and education (3 categories). Abbreviations: AHD: antihypertensive drugs, CCB: calcium channel blockers, ACE: angiotensin converting enzyme, ARB: angiotensin II receptor blockers, HR: hazard ratio, 95% CI: 95% confidence interval.