

Hypertension, atherosclerosis, and fracture risk

Observational investigations with a focus on antihypertensive therapy.

AKADEMISK AVHANDLING

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademien, Göteborgs universitet kommer att offentligen försvaras i sal 2119 på Hälsovetarbacken, Arvid Wallgrens backe, hus 2 ingång F, den 20 maj 2022, klockan 09:00.

av Tove Bokrantz

Fakultetsopponent:

Professor Lars Lind

Institutionen för medicinska vetenskaper,
Uppsala Universitet, Sverige

Avhandlingen baseras på följande delarbeten

- I. Bokrantz T., Ljungman C., Thomas Kahan T., B. Boström K., Jan Hasselström J., Hjerpe P., Mellström D., Schiöler L., Manhem K. Thiazide diuretics and the risk of osteoporotic fractures in hypertensive patients. Results from the Swedish Primary Care Cardiovascular Database. *Journal of Hypertension* 2017; 35(1): 188-197
- II. Bokrantz T., Schiöler L., B. Boström K., Thomas Kahan T., Mellström D., Ljungman C., Hjerpe P., Jan Hasselström J., Manhem K. Antihypertensive drug classes and the risk of hip fracture: results from the Swedish primary care cardiovascular database *Journal of Hypertension* 2020, 38(1): 167-175
- III. Bokrantz T., Manhem K., Lorentzon M., Karlsson M., Ljunggren Ö., Ohlsson C., Mellström D. The association between peripheral arterial disease and risk for hip fractures in elderly men is not explained by low hip mineral density. Results from the MrOS Sweden study. *Submitted to Osteoporosis International*
- IV. Bokrantz T., Manhem K., Lorentzon M., Karlsson M., Ljunggren Ö., Ohlsson C., Mellström D. Hypertension and fracture risk in elderly men, with focus on hip fractures. Observational results from the MrOS Sweden study. *Manuscript*

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Abstract

Aim: To investigate associations between hypertension, arteriosclerotic disease, and fracture risk in adults and the elderly, with a certain focus on how specific antihypertensive drug treatments in patients with high blood pressure might affect the risk for fractures.

Methods and results: In Study I and II, the associations between different antihypertensive treatments and fracture risk were investigated in a cohort of about 60.000 adult women and men diagnosed with hypertension in primary health care. A primary health care database from southern Sweden (SPCCD) linked with national registers was used to identify the cohort, exposure status and fracture outcome from 2006 to 2012. Multivariate Cox proportional hazards models were used to estimate fracture risk across users of different antihypertensive drugs. We found ongoing treatment with thiazide diuretics to be associated with a decreased risk of osteoporotic fractures including hip fractures, compared to other antihypertensive drug therapies. In contrast, treatment with loop diuretics was associated with an increased risk of hip fractures, while the use of beta-blockers, ACE inhibitors, angiotensin receptor blockers, aldosterone receptor blockers, or calcium channel blockers revealed no significant association with fracture risk. The overall findings were similar across men and women, but the decreased fracture risk with thiazides was only statistically significant in men. Study III and IV were based on data from the MrOS Sweden study, a prospective study of elderly men in Gothenburg, Malmö, and Uppsala. Men aged 69-81 years were randomly selected from population registers and invited to participate during the years 2001–2004. Fracture outcomes have been collected since then. Multivariate Cox proportional hazards models were used to estimate the association between (1) peripheral arterial disease and (2) the diagnosis of hypertension at baseline, and hip fractures during follow-up. In Study III, peripheral arterial disease at baseline, defined as an ankle-brachial index <0.9 , was found to be associated with an increased risk of hip fractures independently of age and BMD. In Study IV, no association between hypertension and hip fracture risk during follow-up was found, despite some differences regarding both risk factors and protective factors for fractures between elderly men with and without hypertension.

Conclusions: In summary, fracture risk seems to differ across users of different blood-pressure-lowering drugs. The results support the hypothesis of antihypertensive treatment with thiazide diuretics as a drug that might be beneficial for fracture risk, at least in men. Elderly men with peripheral arterial disease are generally a fragile group of patients with high morbidity, where the study results indicate that these men also have an increased risk of suffering from hip fractures. However, we found no indications that hypertension itself is associated with fracture risk in elderly men.

Keywords: epidemiology, hypertension, antihypertensive agents, fractures, peripheral arterial disease, bone density