Cardiovascular Diseases and Risk of Hip Fracture

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Context Recent studies indicate common etiologies for cardiovascular disease (CVD) and osteoporotic fractures.

Objectives To examine the relation between CVD and risk of hip fracture in twins and evaluate the relative importance of genetics and lifestyle factors in this association.

Design, Setting, and Participants A cohort of all 31,936 Swedish twins born from 1914-1944 was followed up from the age of 50 years. The National Patient Registry identified twins with CVDs and fractures from 1964 through 2005. Time-dependent exposures using Cox proportional hazard regression models were evaluated.

Main Outcome Measure Time to hip fracture after diagnosis of CVD.

Results The crude absolute rate of hip fractures was 12.6 per 1000 person-years after a diagnosis of heart failure, 12.6 per 1000 person-years after a stroke, and 6.6 per 1000 person-years after a diagnosis of peripheral atherosclerosis. The multivariable-adjusted hazard ratio (HR) of hip fracture after a diagnosis of heart failure was 4.40 (95% confidence interval [CI], 3.43-5.63); after a stroke, the HR was 5.09 (95% CI, 4.18-6.20); after a diagnosis of peripheral atherosclerosis, the HR was 3.20 (95% CI, 2.28-4.50); and after an ischemic heart disease event, the HR was 2.32 (95% CI, 1.91-2.84). Identical twins without heart failure and stroke also had, after their co-twins had been exposed to these respective diseases, an increased rate of hip fracture. These sibling twins pseudoexposed for heart failure had a multivariable-adjusted HR of 3.74 (95% CI, 1.97-7.10) for hip fracture, whereas pseudoexposure for stroke had an HR of 2.29 (95% CI, 1.20-4.35).

Conclusions A diagnosis of CVD was significantly associated with risk of subsequent hip fracture. Increased risks in co-twins without an index diagnosis suggest genetic factors in the association between CVD and osteoporotic fractures.

METHODS

Individuals were ascertained from the Swedish Twin Registry, currently the
largest twin registry in the world.12 Twin pairs born between 1914 and 1944 and alive in 1972 were eligible for this study, which resulted in 15,968 pairs. This cohort of twins has been described previously.13 Zygosity information (based on questions about childhood resemblance) was obtained at the time of registry compilation.

Fractures, CVD diagnoses, and comorbidities until December 31, 2005, were determined from the National Patient Registry by International Classification of Diseases (ICD) seventh through tenth edition codes. Cardiovascular disease subdiagnoses studied were heart failure, stroke, ischemic heart disease, and peripheral atherosclerosis (excluding cardiac and cerebral atherosclerosis). We identified hypertension from the registry and self-report data (described below) as a secondary outcome. The National Patient Registry, which was initiated in 1964, covered 83% of the Swedish population in 1972 and all inpatient care in Sweden since 1987. It is updated annually and valid in identifying cases of fracture.14 The proportion of pathological fractures and fractures related to high-energy trauma in elderly persons in Sweden is only about 1%.15,16 Dates of death were based on data from the continuously updated Swedish National Population Register.

Twins entered the study on the date of their 50th birthday (ie, between 1964 and 1994) and were followed up until the date of a first hip fracture, date of death, or end of the follow-up period (December 31, 2005). Twins with previous CVD or hip fracture were excluded. All twins were considered unexposed at study entry and until the date of the first cardiovascular event. Although we observed the twins for more than 40 years, the diagnoses studied in this article are age-related late-onset diseases. Therefore, 92% of the CVDs and 95% of the hip fractures were diagnosed during the past 20 years of follow-up (1986-2005).

A computer-assisted telephone interview was conducted between 1998 and 2000. Questions included items on diseases and symptoms, prescription and nonprescription medication use, occupation, education, physical activity, anthropometric measures, and consumption of alcohol and tobacco. To diminish the risk of period effects, an effort was made to interview members of a twin pair within a month of each other.

The study was approved by the research ethics committee of Karolinska Institutet and the twins gave informed verbal consent to participate in the study.

Statistical Analysis
Kaplan-Meier curves for time-to-hip fracture were plotted for each CVD category. Crude overall rates of hip fracture but also rates within 4 different time frames (≤1, >1-5, >5-10, and >10 years) after each CVD diagnosis are presented.

Cox proportional hazards regression models were used with time-varying exposure of CVD and covariate information to assess hazard ratios (HRs) for hip fracture with 95% confidence intervals (CIs). Co-twin dependences were handled using robust sandwich variance estimates according to Lin and Wei.17 We modeled hip fracture risk after CVD exposure to risk of hip fracture without a CVD diagnosis. First, we fitted a model that included sex as a covariate (all twins were the same age). We then extended the model to include separate marker variables (all dichotomous) for concomitant disorders that were likely covariates of the association between fracture and CVD, including any form of diabetes mellitus, other endocrine disorders, hyperlipidemia, neurologic disease, psychiatric disorder, respiratory diseases, and musculoskeletal disorders, as well as subdiagnoses of CVD. The same number of twins was included in the sex-adjusted model as in the multivariable-adjusted model. Only minor differences were observed in the HRs if we excluded twins with uncertain zygosity information.

Because CVDs are strongly associated with mortality, sensitivity analyses were conducted to check for 2 theoretical and extreme situations that addressed the problem with competing risk from death in that (1) all non-hip fracture patients that died instead had had a hip fracture or (2) all patients were alive at the end of the follow-up period.

Our twin design allowed us to evaluate how genetic factors influence the association between CVD and hip fracture. In this additional analysis, the co-twin (ie, the sibling) without CVD was considered pseudoexposed to CVD from the CVD event in the truly CVD-affected co-twin until censoring or until the pseudoexposed twin sibling experienced a true CVD. The relative hip fracture rates were compared between pseudoexposed and truly exposed twins. Similar estimates would suggest that genes and shared environmental factors are the most important determinants regarding risk of fracture after the CVD event. Estimates in monozygotic and dizygotic twins were compared to investigate the degree of genetic influence.

We additionally estimated age-specific 10-year absolute hip fracture risks. For each subgroup with heart failure, stroke, atherosclerosis, or ischemic heart disease, a Cox proportional hazards model for time to hip fracture was fitted based on age and sex. Predicted sex-specific survival curves were generated for age at CVD diagnosis between 55 and 85 years using 1-year age increments. From each of these survival curves the 10-year absolute risk with 95% CIs was extracted and plotted against age.

To demonstrate the importance of some lifestyle factors (identified from the telephone interview) on the HRs we additionally included in the multivariable model body mass index (BMI) (continuous, calculated as the weight in kilograms divided by height in meters squared), hormone therapy for women (ever/never), impaired balance (yes/no), difficulty to rise from a chair (yes/no), impaired balance (yes/no), impaired balance (yes/no), impaired balance (yes/no), impaired balance (yes/no), impaired balance (yes/no), impaired balance (yes/no), impaired balance (yes/no), impaired balance (yes/no), impaired balance (yes/no), impaired balance (yes/no), impaired balance (yes/no), impaired balance (yes/no), impaired balance (yes/no), impaired balance (yes/no), impaired balance (yes/no), impaired balance (yes/no), impaired balance (yes/no), impaired balance (yes/no), impaired balance (yes/no), impaired balance (yes/no), impaired balance (yes/no), impaired balance (yes/no), impaired balance (yes/no), impaired balance (yes/no), impaired balance (yes/no), impaired balance (yes/no), impaired balance (yes/no), impaired balance (yes/no), impaired balance (yes/no), impaired balance (yes/no), impaired balance (yes/no), impaired balance (yes/no), impaired balance (yes/no), impaired balance (yes/no), impaired balance (yes/no), impaired balance (yes/no), impaired balance (yes/no), impaired balance (yes/no), impaired balance (yes/no), impaired balance (yes/no), impaired balance (yes/no), impaired balance (yes/no), impaired balance (yes/no), impaired balance (yes/no), impaired balance (yes/no), impaired balance (yes/no), impaired balance (yes/no), impaired balance (yes/no), impaired balance (yes/no), impaired balance (yes/no), impaired balance (yes/no), impaired balance (yes/no), impaired balance (yes/no), impaired balance (yes/no), impaired balance (yes/no), impaired balance (yes/no), impaired balance (yes/no), impaired balance (yes/no), impaired balance (yes/no), impaired balance (yes/no), impaired balance (yes/no), impaired balance (yes/no), impaired balance (yes/no), impaired balance (yes/no), impaired balance (yes/no), impaired balance (yes/no), impaired balance (yes/no), impaired balance (yes/no), impaired balance (yes/no), impaired balance (yes/no), impaired balance (yes/no), impaired balance (yes/no), impaired balance (yes/no), impaired balance (yes/no), impaired balance (yes/no), impaired balance (yes/no), impaired balance (yes/no), impaired balance (yes/no), impaired balance (yes/no), impaired balance (yes/no), impaired balance (yes/no), impaired balance (yes/no), impaired balance (yes/no), impaired balance (yes/no), impaired balance (yes/no), impaired balance (yes/no), impaired balance (yes/no), impaired balance (yes/no), impaired balance (yes/no), impaired balance (yes/no), impaired balance (yes/no), impaired balance (yes/no), impaired balance (yes/no), impaired balance (yes/no), impaired balance (yes/no), impaired balance (yes/no), impaired balance (yes/no), impaired balance (yes/no), impaired balance (yes/
converting enzyme inhibitors, β-blockers, and cortisone. In this particular analysis, the outcome variable was hip fracture cases occurring between the date of the telephone interview and the end of the study (December 31, 2005).

Because most persons with hypertension, in contrast to the other cardiovascular diseases in our study, are not identified from the National Patient Registry (with diagnoses from in-patient care), a separate secondary analysis was done for this disorder. We therefore combined the exposure information on hypertension from self-reports during the telephone interview with the information collected from the patient registry. The twins with hypertension were considered exposed from the first date of this diagnosis in the registry or in other cases from the date of the telephone interview.

The number of twins included and excluded in the analyses is given in Figure 1. If the twin had had 2 or more cardiovascular diseases (eg, heart failure and stroke), this twin was included in both the heart failure analysis and in the stroke analysis but if the cardiovascular diseases had occurred at different dates they contributed to different exposure times. This twin was, however, not included in the analyses of the other cardiovascular diseases. Statistical analyses were performed using SAS software version 9.1 (SAS Institute Inc, Cary, North Carolina), Stata 10.1 (Stata Corporation Inc, College Station, Texas), and R (R Foundation for Statistical Computing, Vienna, Austria 2008).

**RESULTS**

Four separate validation studies using genotyping have shown that 95% to 98% of the twin pairs in the study are correctly classified.12 Our cohort included 3487 (21.8%) monozygotic, 5921 (37.1%) same sex dizygotic, and 5607 (35.1%) opposite sex dizygotic twin pairs. Another 953 (6.0%) twin pairs had uncertain zygosity. Of the base sample (n = 31 936), 3663 died before the telephone interview, leaving 28 273 eligible twins to be interviewed. Of these, 24 598 (87%) participated in the interview. Before censoring, 35% of all women and 43% of all men were diagnosed with CVD. Characteristics as a function of cardiovascular diagnosis are presented in Table 1. Individuals with a CVD were, on average, born earlier and had more concomitant diseases. However, only modest differences were observed in anthropometric measures and smoking habits between persons with and without a CVD diagnosis.

Hip fracture after the age of 50 years was diagnosed in 1442 twins (70% of these cases were women). Kaplan-

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**Figure 1. Flow Diagram of Those Included and Excluded from the Study**

The number of twins included and excluded in the analyses of heart failure, stroke, peripheral atherosclerosis, ischemic heart disease, and hypertension. CVD indicates cardiovascular disease.

*Discordant for disease of interest.

*Exclusion algorithm: 1) excluded twins without CVD of interest, 2) excluded twins with hip fracture before the age of 50 years, and 3) excluded twins with a diagnosis of heart failure before the age of 50 years.
Meier curves for the proportion of persons with hip fracture at different ages after a diagnosis of heart failure, stroke, ischemic heart disease, or peripheral atherosclerosis are displayed in Figure 2. The curve for stroke started to diverge from the curve for individuals without a CVD diagnosis early after study entry, whereas the curve for ischemic heart disease started to diverge from the baseline curve 25 years later when the persons were 75 years of age. The crude absolute rate of hip fractures was 12.6 per 1000 person-years for those with ischemic heart disease, compared with 5.2 per 1000 person-years after a stroke, 6.6 per 1000 person-years after a diagnosis of heart failure, 12.6 per 1000 person-years after a diagnosis of peripheral atherosclerosis and 5.2 per 1000 person-years after a diagnosis of ischemic heart disease, compared with 1.2 per 1000 person-years for those without a CVD diagnosis.

Within the first year after diagnosis of both heart failure and stroke (Figure 3), the hip fracture rate was higher than the more distant time frames despite that the twins had achieved an older age and hence were more likely to experience hip fracture during the latter periods. The higher rates after a recent diagnosis, however, were not observed in ischemic heart disease and peripheral atherosclerosis.

All cardiovascular diagnoses were associated with increased hip fracture risk independent of the other CVD diagnoses investigated and other comorbidities (Table 2). Thus, in comparison with individuals without CVD, heart failure gave a multivariable-adjusted HR of 4.40 (95% CI, 3.43-5.63) for hip fracture; individuals with a stroke had an HR of 5.09 (95% CI, 4.18-6.20). The elevated hip fracture rate was present after ischemic stroke (HR, 4.95; 95% CI, 4.07-6.02) and hemorrhagic stroke (HR, 5.48; 95% CI, 3.68-8.15). Peripheral atherosclerosis (HR, 3.20; 95% CI, 2.28-4.50) and ischemic heart disease (HR, 2.32; 95% CI, 1.91-2.84) also conferred higher risk of hip fracture. If the diagnosis of ischemic heart disease was restricted to individuals with acute myocardial infarction, an increased risk was also seen (HR, 2.42; 95% CI, 1.85-3.17). Cardiovascular disease was associated with an increased relative hip fracture rate to a comparable level in both men and women except after stroke, for which the fracture rate tended to be higher in men (HR, 6.65; 95% CI, 4.82-9.19) than in women (HR, 4.42; 95% CI, 3.49-5.61)

Identical twins without heart failure and stroke also had an increased rate of hip fracture after their co-twins were exposed to these respective diseases. Thus, a pseudoeposure of heart failure in identical twin siblings was associated with a 4-fold increased hip fracture rate as compared with those without CVD (Table 3). Moreover, identical twins pseudoeXposed to stroke had a doubled hip fracture rate after the stroke event in the co-twin. These increased risks were less pronounced in pseudoeXposed dizygotic siblings. Overall, we also found that sibling pseudoeXposure to ischemic heart disease and peripheral atherosclerosis conferred increased hip fracture rates; however, we

Table 1. Selected Characteristics as a Function of Cardiovascular Disease

<table>
<thead>
<tr>
<th>No (%) of Participants</th>
<th>No CVD (n = 19089)</th>
<th>Heart Failure (n = 2270)</th>
<th>Stroke (n = 2962)</th>
<th>Peripheral Atherosclerosis (n = 1061)</th>
<th>Ischemic Heart Disease (n = 4869)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth year (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at the CVD, mean (SD), yrs</td>
<td>NA</td>
<td>74.4 (8.2)</td>
<td>70.5 (9.0)</td>
<td>69.0 (9.2)</td>
<td>67.9 (9.0)</td>
</tr>
<tr>
<td>BMI, mean (SD)</td>
<td>25.0 (3.3)</td>
<td>25.7 (3.7)</td>
<td>25.3 (3.0)</td>
<td>25.1 (3.3)</td>
<td>25.6 (3.1)</td>
</tr>
<tr>
<td>Men</td>
<td>8408 (44.0)</td>
<td>1254 (55.2)</td>
<td>1605 (54.2)</td>
<td>597 (56.3)</td>
<td>2944 (60.5)</td>
</tr>
<tr>
<td>Women</td>
<td>10 681 (56.0)</td>
<td>1016 (44.8)</td>
<td>1357 (45.8)</td>
<td>464 (43.7)</td>
<td>1925 (39.5)</td>
</tr>
<tr>
<td>Current</td>
<td>2244 (14.7)</td>
<td>203 (12.3)</td>
<td>286 (13.1)</td>
<td>162 (20.9)</td>
<td>469 (12.4)</td>
</tr>
<tr>
<td>Leisure physical activitya</td>
<td>Sedentary</td>
<td>3001 (19.6)</td>
<td>468 (27.8)</td>
<td>494 (22.6)</td>
<td>234 (30.2)</td>
</tr>
<tr>
<td></td>
<td>Moderate exerciseb</td>
<td>10740 (70.3)</td>
<td>1135 (69.0)</td>
<td>1576 (72.1)</td>
<td>498 (64.3)</td>
</tr>
<tr>
<td></td>
<td>Heavy exerciseb</td>
<td>1540 (10.1)</td>
<td>53 (3.2)</td>
<td>116 (5.3)</td>
<td>42 (5.4)</td>
</tr>
<tr>
<td>Impaired balanceb</td>
<td>1197 (7.8)</td>
<td>323 (19.6)</td>
<td>482 (22.0)</td>
<td>160 (20.7)</td>
<td>629 (16.6)</td>
</tr>
<tr>
<td>Difficulty rising from a chaira</td>
<td>1469 (9.6)</td>
<td>310 (18.8)</td>
<td>383 (17.5)</td>
<td>155 (20.7)</td>
<td>600 (15.8)</td>
</tr>
<tr>
<td>Ever use of hormone therapy in womenb</td>
<td>3771 (43.0)</td>
<td>177 (24.0)</td>
<td>240 (23.8)</td>
<td>91 (26.0)</td>
<td>496 (32.8)</td>
</tr>
<tr>
<td>Heart failurec</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular diseasesc</td>
<td>Cerebrovascular lesion</td>
<td>NA</td>
<td>586 (25.8)</td>
<td>309 (29.1)</td>
<td>1034 (21.2)</td>
</tr>
<tr>
<td>Ischemic heart diseasec</td>
<td>NA</td>
<td>1416 (62.4)</td>
<td>1053 (35.6)</td>
<td>504 (47.5)</td>
<td>NA</td>
</tr>
<tr>
<td>Acute myocardial infarctionc</td>
<td>NA</td>
<td>904 (29.8)</td>
<td>633 (21.4)</td>
<td>317 (29.9)</td>
<td>2840 (54.2)</td>
</tr>
<tr>
<td>Peripheral atherosclerosisc</td>
<td>NA</td>
<td>336 (14.8)</td>
<td>321 (10.8)</td>
<td>515 (10.6)</td>
<td></td>
</tr>
<tr>
<td>Hypertensionc</td>
<td>NA</td>
<td>800 (35.2)</td>
<td>1092 (36.9)</td>
<td>422 (39.8)</td>
<td>1532 (31.5)</td>
</tr>
<tr>
<td>Cancerc</td>
<td>2757 (14.4)</td>
<td>463 (20.4)</td>
<td>530 (17.9)</td>
<td>228 (21.5)</td>
<td>905 (18.6)</td>
</tr>
<tr>
<td>Endocrinecd</td>
<td>1224 (6.4)</td>
<td>984 (43.4)</td>
<td>1023 (34.5)</td>
<td>432 (40.7)</td>
<td>1798 (36.9)</td>
</tr>
<tr>
<td>Musculoskeletal skeleton disorderc</td>
<td>2650 (13.6)</td>
<td>747 (22.9)</td>
<td>832 (28.1)</td>
<td>348 (32.8)</td>
<td>1333 (27.4)</td>
</tr>
<tr>
<td>Psychiatric diseasec</td>
<td>1742 (9.1)</td>
<td>537 (23.7)</td>
<td>662 (22.4)</td>
<td>223 (21.0)</td>
<td>855 (17.6)</td>
</tr>
<tr>
<td>Neurologic disorderc</td>
<td>907 (4.8)</td>
<td>375 (16.5)</td>
<td>728 (24.6)</td>
<td>207 (19.3)</td>
<td>698 (14.3)</td>
</tr>
<tr>
<td>Respiratory diseasec</td>
<td>1511 (7.9)</td>
<td>1152 (50.7)</td>
<td>918 (31.0)</td>
<td>405 (38.2)</td>
<td>1666 (34.2)</td>
</tr>
</tbody>
</table>
| Abbreviation: BMI, body mass index, calculated as the weight in kilograms divided by height in meters squared; NA, not applicable. aAmong those who participated at the telephone interview (n = 15 281 for those with no CVD, n=1646 for heart failure, n=2186 for stroke, n=774 for atherosclerosis, and n=3791 for ischemic heart disease. The number of responding women was respectively 8765, 738, 1008, 350, and 1513. bIt includes leisure physical activity (defined as walking and gardening) and moderate physical training. cIdentified from the National Patient Registry.

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had a limited number of hip fractures in the subgroup of identical twins.

Ten-year absolute risks of hip fracture in relation to sex and age at CVD diagnosis are depicted in Figure 4. A higher risk of hip fracture was observed in women at all ages and in all CVD categories. The average 75-year-old woman had an 18% (95% CI, 13%-22%) risk of hip fracture within 10 years after diagnosis of heart failure, whereas the corresponding estimate was 10% (95% CI, 7%-14%) in a man of the same age. A 75-year-old woman with a stroke had a 10-year risk of hip fracture of 19% (95% CI, 15%-23%), whereas a man of the same age had a risk of 15% (95% CI, 12%-19%).

Hypertension, as diagnosed based on self-reports and register data, was also associated with an increased hip fracture risk with a sex-adjusted HR of 1.42 (95% CI, 1.23-1.64) and a multivariable-adjusted HR of 1.59 (95% CI, 1.36-1.85).

We analyzed hip fracture risk in twins who had participated in the telephone interview. Using this approach, we had the possibility to include lifestyle factors, medication use, and body stature to our multivariable model. This comprehensive multivariable model only marginally affected our parameter estimates of hip fracture risk after an event of CVD; thus, these results are not presented.

In sensitivity analyses, when twins who had died were classified as having had a hip fracture, multivariable-adjusted HRs for hip fracture ranged from 9.78 (95% CI, 8.99-10.64) for heart failure to 3.69 (95% CI, 3.42-3.98) for ischemic heart disease. At the other extreme, when those who died without experiencing a hip fracture were observed to the end of the follow-up period, the HRs ranged from 3.89 (95% CI, 3.21-4.70) for stroke to 1.97 (95% CI, 1.60-2.43) for ischemic heart disease.

**COMMENT**

Our population-based twin study demonstrated an increased rate of hip fracture after different major cardiovascular events in both women and men. The high absolute 10-year risk of hip frac-
ture after CVD was more prominent in women even though we found no differences in relative rates for hip fracture between the sexes, and even a higher relative risk for hip fracture after a diagnosis of stroke in men. The previously recognized lifetime risk of hip fracture independent of CVD status in women is twice that of men. We advocate that individuals with a recent diagnosis of CVD should have their future fracture risk evaluated with clinical risk factors and bone scans (eg, by the recently established 10-year probability using the World Health Organization fracture risk assessment tool [FRAX] algorithm). Furthermore, it should be emphasized that our estimates were independent of previously recognized clinical risk factors of hip fracture and a diagnosis of CVD would most probably add risk to those factors.

An increased hip fracture risk for the pseudoexposure in the co-twin analyses, particularly in identical twins, is an indication that genes predispose to the development of CVD and fractures. Most of the overall increased rate of hip fracture after heart failure (and part of the increased risk after stroke) appears to be explained by genes or by early environmental sharing (ie, not individual lifestyle habits or other individual-specific environmental factors).

Our study was not designed to fully elucidate the common pathophysiological mechanisms that CVDs and hip fracture share. The genetic factors that might explain our associations include not only telomere length but also specific genes involved in cellular mechanisms shared by the vasculature and bone. Matrix proteins supporting bone, vessel walls, and the myocardium can be of special relevance. Other potential factors are calcification regulatory hormones, sex steroids, proteins related to lipid metabolism, oxidative stress, and chronic inflammation.

In addition to their vulnerability to fractures through direct influences on bone, persons with CVDs could have a greater propensity for falls. There is a higher tendency for men to fall after a stroke, which could explain our higher relative rates of hip fracture in men. The genetic influence measured as pseudoexposure was less dominant after a diagnosis of stroke than for heart failure, which could, in part, be explained by the increased propensity to falls after a stroke. Additionally, balance disturbances may have occurred as adverse effects of medication, leading to falling accidents. However, this is not likely the most plausible explanation because there is no increased risk of fracture with cardiovascular drug treatment and because most of the increased rate of hip fracture after CVD was mediated by genetic causes in common for the diseases.

We found the highest hip fracture rates early after diagnosis of heart failure or stroke. Such rates have previously been observed after stroke but not after heart failure. The time course of the hip fracture rate may have been partially related to immobilization after the CVD event. A concomitant decrease in muscle strength and postural stability may increase the risk for falls but subsequently for fractures. Moreover, immobilization increases the rate of bone loss that can further increase the risk of fracture. Increased bone loss has been observed after the diagnosis of heart failure, hypertension, and stroke. The severity of the cardiovascular diagnoses, which we were not able to address in this study, can be of importance in relation to fracture risk. A more severe CVD is associated with higher mortality, which constitutes a competing risk for fracture. The sensitivity analysis, which addressed the problem with competing risk from death, indicates that our estimates are not likely to be exaggerated; rather, the contrary is true.

Our results extend the findings from epidemiologic studies examining the association between CVD and fracture risk. In a prospective study in women, Bagger et al verified the cross-sectional finding of Schulz et al that severe aortic calcifications increased the relative risk of hip fracture 2-fold to 3-fold. In contrast, a recent Framingham Heart Study report indicated that the severity of aortic calcifications did not significantly affect hip fracture rate. The 35-year-long duration of the follow-up, however, might have concealed a

| Table 2. Hazard Ratios of Hip Fracture Associated With Different Cardiovascular Diseases |
|-------------------------------------|---------------------------------|----------------------------|----------------------------|
| Heart Failure                      | Stroke                          | Peripheral Atherosclerosis | Ischemic Heart Disease     |
| No. of hip fracture cases with CVD |                                 |                            |                            |
| Exposed, person-years              | 8931                            | 17,313                     | 6,288                      |
| No CVD, person-years               | 430,041                         | 437,461                    | 396,356                    |
| Sex-adjusted model, HR (95% CI)   | 3.04 (2.42-3.81)                | 3.86 (3.25-4.59)           | 2.04 (1.50-2.79)           |
| Multivariable model, HR (95% CI)  | 4.40 (3.43-5.63)                | 5.09 (4.18-6.20)           | 3.20 (2.28-4.50)           |

Abbreviations: CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio.

a No CVD group was used as reference group (includes 528 twins with hip fracture).

b Adjusted for sex, endocrine disorder, neurological disease, psychiatric disorder, respiratory disease, musculoskeletal disorder, hypertension, diabetes mellitus, heart failure, stroke, peripheral atherosclerosis, ischemic heart disease, and hypertension (all dichotomous).
potential association between aortic calcification and risk of hip fracture. In the present study and in a case-control study in women by our team, we observed the greatest fracture rates after a recent diagnosis of CVD. We also demonstrated that the association between CVD and hip fracture risk in the case-control study was dependent on the diagnosis of CVD. Furthermore, in the same study, the excess risk of hip fracture, independent of comorbidity and lifestyle habits, was most prominent after a diagnosis of heart failure, hypertension, or stroke and less obvious after ischemic heart disease or peripheral atherosclerosis. The present cohort study confirms that these CVDs are associated with an increased hip fracture risk.

Table 3. Hazard Ratios of Hip Fracture for Pseudoexposure of Different Cardiovascular Diseases by Zygosity

<table>
<thead>
<tr>
<th>Type of Pseudoexposure</th>
<th>Monozygotic Twins (n=3487)</th>
<th>Dizygotic Twins (n=11 528)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Heart Failure</td>
<td>Stroke</td>
</tr>
<tr>
<td>No. exposed</td>
<td>196</td>
<td>304</td>
</tr>
<tr>
<td>No. of hip fracture cases among exposed</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>No. at risk, exposed, person-years</td>
<td>1598</td>
<td>2736</td>
</tr>
<tr>
<td>No. of hip fracture cases among nonexposed</td>
<td>87</td>
<td>103</td>
</tr>
<tr>
<td>No. at risk, nonexposed, person-years</td>
<td>70 722</td>
<td>75 757</td>
</tr>
<tr>
<td>Sex-adjusted model, HR (95% CI)</td>
<td>3.41 (1.80-6.45)</td>
<td>1.99 (1.05-3.76)</td>
</tr>
<tr>
<td>Multivariable model, HR (95% CI)</td>
<td>3.74 (1.97-7.10)</td>
<td>2.29 (1.20-4.35)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; HR, hazard ratio.

Ten-year probabilities of hip fracture by age at time of diagnosis of cardiovascular disease. Shaded areas indicate 95% confidence intervals.

Figure 4. Risk of Hip Fracture by Age and Sex

The reliability of our results depends on the quality of the register data. The unique personal identity number used in Sweden made it possible to link individual prospective data on diseases treated during hospitalization through the nationwide and complete National Patient Registry. With this registry, there is virtually no loss to follow-up. The overall quality of this registry as well as the validity of the CVD data are considered high.35,36 After the first event of acute stroke, the diagnosis could be confirmed in 94% of the cases: for heart failure, the corresponding figure was 95%. Thus, the impact of diagnostic misclassification is probably modest. However, in addition to no information on severity of the CVD, the ability to detect CVDs, diagnostic criteria for diagnoses, and treatments have...
changed over our long follow-up, with the strong possibility of conservative biased estimates as a consequence. Our study has additional strengths, including a population-based design, a large number of CVD events and fractures, inclusion of men and women, complete follow-up, and extensive covariate data. Information on body weight, smoking, medication, physical fitness, and physical activity level, however, was obtained in only a subgroup and by telephone interview. Changes in these variables during follow-up were not considered in our study. Another limitation is that the pseudoexposure analyses in the identical twins included few hip fracture cases that led to unstable estimates. The analyses with a higher number of fractures in dizygotic twins, however, gave supportive results, i.e., the increased risk of hip fracture after a CVD seems to be partially genetic.

Clinicians should be aware of the considerably increased rate of hip fracture in both sexes, especially after a recent hospitalization for CVD. Genetic predisposition is probably a major determinant of the excess fracture rate.

Author Contributions: Dr Michaëllson had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Acquisition of data: Melhus, Pedersen, Michaëllson.

Analysis and interpretation of data: Sennerby, Melhus, Gedeberg, Byberg, Garmo, Ahlbom, Pedersen, Michaëllson.

Drafting of the manuscript: Sennerby, Michaëllson.

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Administrative, technical, or material support: Sennerby, Pedersen, Michaëllson.

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