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Associations of Hip Fracture and Stroke in Older Adults

Occurrence, risk, and prognosis

PhD dissertation

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List of papers

The thesis is based on the following four original studies, which will be referred to in the following text by their Roman numerals (I-IV). The studies are attached in the corresponding appendices, I-IV.

I. **Association of CHA_2DS_2 -VASc Score with Stroke, Thromboembolism, and Death in Hip Fracture Patients**
Hjelholt TJ, Johnsen SP, Brynningsen PK, Pedersen AB. *Journal of the American Geriatrics Society.* Volume 68, 8, 2020, s. 1698-1705. DOI: 10.1111/jgs.16452

II. **Development and validation of a model for predicting mortality in patients with hip fracture.**
Hjelholt TJ, Johnsen SP, Knudsen JS, Prieto-Alhambra D, Pedersen AB. *Age and Ageing*. 2022;**51.** DOI: 10.1093/ageing/afab233

III. **The interaction effect between previous stroke and hip fracture on postoperative mortality. A nationwide cohort study**
Hjelholt TJ, Johnsen SP, Brynningsen PK, Pedersen AB. *Clin Epidemiol.* 2022, Vol. 14, Pages 543-553. DOI: 10.2147/CLEP.S361507

IV. **Impact of stroke history on the risk of recurrent hip fracture or major osteoporotic fractures among patients with incident hip fracture. A nationwide cohort study**
Hjelholt TJ, Johnsen SP, Brynningsen PK, Andersen G, Pedersen AB. *Submitted to Journal of Bone and Mineral Research*

Abbreviations

AF:	Atrial fibrillation
BMI:	Body Mass Index
CAS:	Cumulated ambulation score
CCI:	Charlson Comorbidity Index
CHA_2DS_2-VASc:	Congestive heart failure, hypertension, age ≥75 years (2 points), diabetes, previous stroke/TIA/systemic embolism (2 points), vascular disease, age 65-74 years and female sex
CI:	Confidence interval
DAGs	Directed acyclic graphs
DMHFR:	Danish Multidisciplinary Hip Fracture Registry
DOACs:	Direct-acting oral anticoagulants
IR:	Incidence rate
MICE:	Multiple imputation by chained equations
MR:	Mortality rate
NHFS:	Nottingham Hip Fracture Score
NPR:	National Patient Registry
OAC:	Oral anticoagulant treatment
OR:	Odds ratio
PPV:	Positive predictive value
PY:	Person year
TIA:	Transient ischemic attack

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1. Introduction

Hip fracture and stroke constitute two of the most severe diseases affecting older individuals. Both diseases have a substantial impact on mortality, and survivors experience increased disability, such as reduced mobility, cognition, and level of function.[1,2] Osteoporotic fractures alone, of which hip fractures are the most fatal type, are responsible for a higher loss of disability-adjusted life years than most common types of cancer and is estimated to represent 1.75% of the total burden of disease in Europe.[3] Strokes constitute an even higher burden – approximately 5% of the total loss of disability-adjusted life years worldwide.[4,5] As age is strongly associated both conditions, the incidence is expected to increase in the coming decades, mainly due to population demographics.[6-8] Consequently, besides being a considerable threat to older individuals' well-being, these diseases place a substantial economic burden on the national healthcare systems.[4,9]

Although an increased risk of poststroke hip fracture and post hip fracture stroke has been described in previous studies,[10,11] it generally receives little clinical attention. This thesis aims at describing the association between hip fracture and stroke with the objective of identifying potential areas for targeted prevention and obtaining a more in-depth understanding of the interplay between the two diseases (Figure 1). In the following, an introduction is given to current knowledge about hip fracture and stroke epidemiology and treatment and the known links between the two diseases. Subsequently, an introduction is given to each of the four studies. After this, the key methodological aspects of the studies are described, the main results are presented, and, finally, the methodological issues and the clinical implications of the findings are discussed.

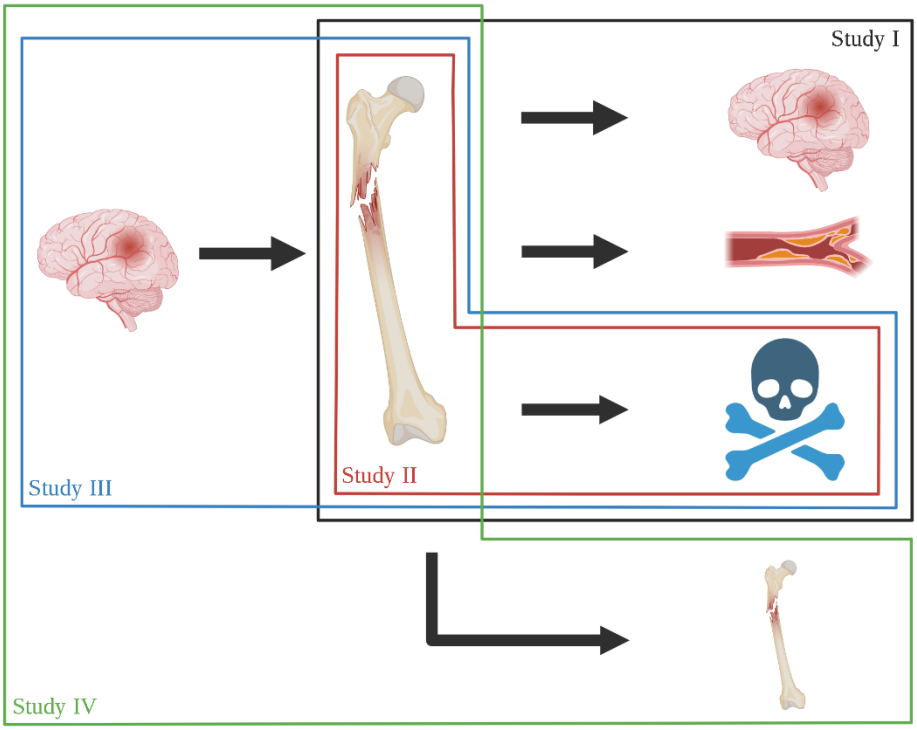


Figure 1. *Thesis outline indicating the investigated associations. Black line: Study I; investigation of risk factors for postoperative stroke, thromboembolism, and mortality. Red line: Study II; development of a prediction model for 1-year mortality of patients with hip fracture. Blue line: Study III; Risk of mortality in patients with/without hip fracture and with/without stroke history. Green line: Study IV; Risk of recurrent fracture in patients with incident hip fracture with/without prefracture stroke history. Figure created with BioRender.com*

2

2. Background

2.1. Hip fracture

Approximately 6,500 persons aged 65 years or older sustain a proximal femur fracture every year in Denmark; this corresponds to an incidence rate (IR) of 4.2 per 1,000 person years (PYs)[12,13] – one of the highest incidences in the world.[14] Proximal femur fracture, commonly referred to as hip fracture, is one of the most frequent and most severe types of fracture among older individuals. Three main subtypes are usually described:[15] Intracapsular fracture of the femoral neck (medial fractures), comprising around 50% of all hip fractures, and extracapsular (lateral) fractures, which are further subdivided into trochanteric fractures (40% – 45%) and subtrochanteric fractures (around 5%). The vast majority of hip fractures in older persons are related to a low-energy trauma such as falls on the same level, indicating that osteoporosis is an underlying condition.[16] As the risk of falling and the risk of osteoporosis increase with age, patients with hip fractures are often relatively old (mean age of 82 years), approximately two thirds are women, and almost 70% have other chronic diseases.[12] The proportion of patients with hip fracture that has comorbidities at the time of fracture has risen dramatically in the past decades.[12] This indicates that patients are increasingly likely to have cognitive or physical deficits, which can possibly augment the risk of complications. Projections of hip fracture incidences have estimated a worldwide rise from 1.7 million in 1990 to 6.3 million in 2050 – mainly as a result of population aging.[16,17]

The prognosis following hip fracture is unfavorable. Postoperative mortality is around 10% within 30 days, rising to 25% – 30% in 1 year.[12] The most frequent postoperative complications include reoperation (5% – 10% within 1 year),[18,19] infections (10% within 15 days),[20] and cardiovascular events - including both venous and arterial thromboembolisms (1% – 3% within 30 days).[11,21,22] Despite rehabilitation in the early postoperative phase, 50% of patients do not regain their walking ability within 6 months.[16] Depending on age, level of comorbidity, and prefracture physical function, the disabilities following hip fracture become chronic in 30% – 60% of cases, which increases dependence on basic personal and domestic help.[23] Permanent institutionalization in nursing homes is a reality for 10% – 20% of individuals in the first postoperative year.[23]

2.1.1. Hip fracture treatment

Clinically, patients having sustained a hip fracture need both surgical and geriatric treatment. As far as surgery is concerned, the first efficacious osteosynthesis was performed in 1875,[24] and experiments with insertion of arthroplasties became successful in the 1920s and 1930s.[25] Since then, the field of hip fracture surgery has undergone tremendous development. Current national and international guidelines are still developing as new research is conduced;[15,26] however, a general consensus exists on recommendations to use surgical techniques that 1) allow patients to bear full weight immediately after surgery and 2) to operate

patients as fast as their condition allows – preferably within 24 hours. The surgical procedure offered to the patient depends on the type of fracture and the degree of dislocation and includes 1) osteosynthesis using parallel screws or arthroplasty (hemi- or total) for intracapsular fractures, 2) internal fixation using extramedullary material for trochanteric fractures, and 3) internal fixation with an intramedullary nail for subtrochanteric fractures. The choice between osteosynthesis or arthroplasty for intracapsular fractures also depends on the patient's age, cognitive status (ability to comply with movement restrictions), and prefracture mobility level; the younger and fitter patients achieve better results from osteosynthesis, whereas the older and frailer patients benefit from arthroplasty. Finally, for patients with very short life expectancy such as immobilized patients with end-stage dementia, a Girdlestone operation (resection of proximal femur, allowing the remaining end to dislocate into the soft tissue) or conservative treatment with a pain catheter can be considered as a palliative strategy.[15]

The choice of anesthesia for hip fracture surgery has been debated in recent decades without a clear consensus having emerged. Generic guidelines for anesthesia increasingly recommend spinal anesthesia over general anesthesia; however, this has not proven favorable in patients undergoing hip fracture surgery, possibly because the choice of anesthesia has less impact on patient prognosis than many other factors including timely surgery,[27,28] swift mobilization and rehabilitation, and state-of-the-art orthogeriatric care.[28] Current guidelines recommend intraoperative local analgesia to reduce postoperative systemic analgesic needs. Furthermore, regardless of neuroaxial or general anesthetic techniques, it is recommended to minimize dosage of anesthetic drugs as much as possible to reduce the risk of intraoperative hypotension and postoperative delirium.[28]

Besides the apparent need for surgical mending of the fractured femur and initiation of rehabilitation, other geriatric tasks must be undertaken, such as preoperative optimization of medical conditions, diagnosing and treating osteoporosis, handling comorbidities and complications, and prioritizing diagnostic efforts to identify the reason for falling. This insight gave rise to the development of "orthogeriatric care", a multidisciplinary team approach developed in England in the 1950s.[29] The beneficial effect of orthogeriatric care has been firmly established,[30] and this approach and simultaneous general advances in diagnostic and treatment possibilities throughout the last part of the 20th century have collectively considerably improved the prognosis in patients with hip fracture.[12]

With the intention to strengthen this positive development even more as we progressed into the new millennium, implementation of audit programs began in many industrialized countries. These initiatives utilize a multidisciplinary team consisting of healthcare professionals within the relevant specialties, such as orthopedic surgeons, anesthetists, geriatricians, nurses, physiotherapists, occupational therapists, and epidemiologists, to monitor the entire patient pathway and improve the quality of care and prognosis of

patients with hip fracture. In Denmark, the National Indicator Project for hip fracture began the development of standards of care in 2000.[31] Later, the Danish Multidisciplinary Hip Fracture Registry (DMHFR), which was launched in 2003,[32] has taken over responsibility for continuously developing and maintaining standards of care and performing national audits. However, despite these efforts, controversy exists as to whether the positive temporal trend in mortality following hip fracture continues or not.[33] According to published data from Denmark, mortality seems to have remained relatively stable during the past couple of decades,[12,32,34] perhaps because increasing age and increasing comorbidity of the population outweigh the benefits of the therapeutic advancements.[35-37]

2.2. Stroke

Stroke is one of the most severe manifestations of cardiovascular disease.[1,38] It is an umbrella definition that includes cerebral infarction (ischemic stroke) and spontaneous intracerebral and subarachnoid bleeding (hemorrhagic strokes). The pathophysiology of stroke subtypes differs; ischemic stroke is predominantly a consequence of intracranial small-vessel atherosclerosis, resulting in *in situ* thrombosis, or embolic events due to atrial fibrillation (AF) or atherosclerosis of major arteries.[1] Hemorrhagic stroke most often occurs due to arterial hypertension or cerebral amyloid angiopathy, resulting in deep-perforating artery rupture (intracerebral hemorrhage) or rupture of an intracranial aneurism into the subarachnoid space (subarachnoid hemorrhage). Finally, side effects from antithrombotic medication is an increasingly frequent cause of hemorrhagic stroke.[1,39-41]

Among older patients, ischemic stroke is the most common type with IRs of 500-1000 per 100,000 PYs.[39] The hemorrhagic types are less common; IR of 50-150 per 100,000 PYs for intracerebral hemorrhage[39] and 6-7 per 100,000 PYs for subarachnoid hemorrhage.[41] It is estimated that 90% of all strokes are due to modifiable risk factors, especially hypertension, smoking, diabetes, hyperlipidemia, and physical inactivity. In addition, AF is an important risk factor for ischemic stroke[1]. Increasing age is the most important non-modifiable risk factor.[1] Interestingly, stroke incidence among older adults is reported to be stable or slightly decreasing in most high-income countries.[1,5] This is also corroborated in a recent Danish study.[39] Variation in incidences across countries is believed to be a result of a varying prevalence of the different risk factors.[5,39]

The prognosis is poor for any type of stroke; patients with ischemic stroke have a 30-day and 1-year mortality risk comparable to that of patients with hip fracture (age-specific estimates, 65-90+ years, 30 days: 5% – 30%, 1 year: 20% – 50%),[39,42] whereas the prognosis following hemorrhagic stroke is even worse (overall, 30 days: 24% – 27%, 1 year: 35% – 37%).[40] The higher mortality in patients with hemorrhagic strokes is explained mainly by the mass effect of the hematoma and the sub-acute edema that subsequently occur. Some of the most well-described prognostic factors of both functional outcomes and mortality include the severity of the stroke and the patient's age and comorbidity burden.[39]

2.2.1 Stroke treatment

Overall, mortality following all types of strokes has decreased considerably. Since the mid-'90s, the 30-day mortality has been reduced by 35% – 45%.[43] This decline is largely attributed to improvements in stroke care of two kinds. First, endovascular treatment possibilities for ischemic stroke were introduced in 1995; second, focus has shifted to faster diagnosis and treatment, prehospital staff's awareness of stroke symptoms has increased, and the organization of emergency departments with specialized acute stroke units has improved; all of which has profoundly reduced time from symptom onset to treatment.[1,43-47] In addition, community education programs to increase recognition of stroke symptoms among laymen have also contributed to the reduced treatment delay.[1]

Ischemic strokes are primarily treated with intravenous thrombolysis, although endovascular thrombectomy has proven more efficacious if administered without delay to patients with large-artery occlusions – and as this technology improves, more distant occlusions become accessible.[1] In the case of intracerebral hemorrhage, the main treatment is a lowering of the systolic blood pressure and reversal of anticoagulation if relevant. Surgical intervention to alleviate intracranial pressure and evacuate the hematoma may be indicated.[1] For subarachnoid hemorrhage, coiling of the ruptured aneurism is often necessary.[41] Despite the therapeutic advancements and the improved prognosis, stroke potentially has catastrophic consequences for the individual and it remains a leading cause of death and disability among adults worldwide.[1,48,49] With more patients surviving a stroke, the growing need for proper handling of the disabilities and risk of complications following stroke has become apparent.[50,51]

A national program for development of clinical guidelines and monitoring of stroke care was initiated under the National Indicator Project in 2000.[31] Subsequently, a clinical quality database, *The Danish Stroke Registry,* has taken over the continuous development and monitoring of stroke care in Denmark.[52]

2.3. Associations of osteoporotic hip fractures and stroke

Documentation of the increased risk of osteoporosis and hip fracture following stroke is plentiful,[53-58] and the topic has been the subject of several reviews and meta-analyses.[10,59,60] The association may partly be due to shared risk factors (e.g. age, smoking, and inactivity)[61] and partly a consequence of stroke sequelae such as cognitive impairment and hemiplegia, heightening the fall risk and accelerating bone loss on the hemiplegic side[56] – indeed, 60% – 80% of poststroke hip fractures occur on the patient's paretic side.[53,54,62] Furthermore, atherosclerosis in vessels supplying the bone tissue has proven to cause bone loss.[63] In addition, common pathophysiological mechanisms of atherosclerosis and osteoporosis, including pro-inflammatory cytokines and bone-regulatory factors, may contribute to the association.[61,64] Consequently, osteoporosis screening and assessment of vitamin D status are recommended in stroke rehabilitation guidelines,[65] although only in the

oldest and frailest part of the population. Several reports therefore strongly recommend increased attention to this matter.[10,56,66,67]

An equally increased risk of postoperative stroke among patients with hip fracture is also found, despite guideline-recommended thromboembolic prophylaxis.[11] The risk factors and mechanisms causing this increased stroke risk have only been sparsely evaluated, but current knowledge suggests several possible reasons for this association. As described for poststroke hip fracture, shared risk factors and pathophysiological mechanisms may be contributing elements, as stroke risk factors undoubtedly are prevalent in this patient group. Other aspects such as an increased pro-coagulant state caused by the trauma and surgery[68,69] may further increase the risk of thrombosis. Venous thromboembolic prophylaxis is routinely administered and decreases the risk to a certain extent,[70] but, evidently, this routine only *reduces* the risk – it does not *remove* it.[11,22] Finally, the cementation of prosthesis material may give rise to the bone cement implantation syndrome[71-75] in which the high intramedullary pressure during cementation can lead to transient hypotension and formation of emboli. This potentially leads to clinical stroke in two ways: 1) hypoxia and systemic hypoperfusion can impede cerebral blood flow; a risk that increases with age as the cerebral blood flow autoregulation becomes less efficient[76] and border zone infarcts may thus arise;[77] 2) embolic material may be shunted to the left side of the circulation either through a patent foramen ovale or by transit through recruitable pulmonary shunts.[72,74] In the worst cases of bone cement implantation syndrome, complete circulatory collapse has been observed.[78] Consequently, guidelines for perioperative blood pressure management emphasize extra attention when the femoral canal is manipulated.[28] Risk factors, incidence, and the clinical consequences of bone cement implantation syndrome are only sparsely described in previous studies, why the relative importance of these factors remains largely unknown.

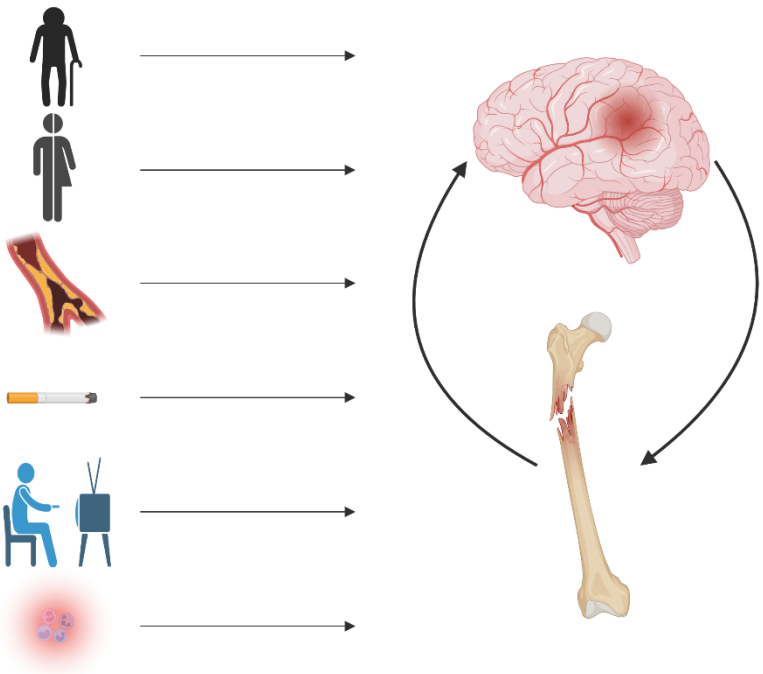


Figure 2. *Illustration of known shared risk factors for stroke and hip fracture (age, sex, atherosclerosis, smoking, inactivity, and inflammation) = "parallel association", and the increased risk of both events following one of them = "circular association".* Figure created with *BioRender.com*

In summary, current knowledge outlines both a "parallel" association of hip fracture and stroke due to shared risk factors and pathophysiological mechanisms but also a "circular" association of hip fracture and stroke, i.e., sustaining one of the conditions increases the risk of encountering the other (Figure 2). Several questions, however, remain unanswered.

2.4. Other thromboembolic events

Besides thromboembolic events in the cerebral circulation, reports of an increased risk of other kinds of arterial thromboembolism – mainly myocardial infarction – indicate that patients undergoing hip fracture surgery have a higher susceptibility to arterial thromboembolism in general.[11,79-81] The pathophysiological mechanisms are primarily believed to be the same as for patients sustaining a peri- or postoperative stroke, although coronary vasospasm and increased shear stress during anesthesia weaning are likely to contribute to the risk of myocardial infarction.[82]

Despite timely administration of perioperative thromboprophylaxis, the risk of postoperative venous thromboembolism is also markedly increased in the early postoperative period and up to 1 year after hip fracture.[22] This risk is substantially elevated among patients with comorbidity,[22] by prolonged bed rest,[83] by use of certain medications such as corticosteroids,[84] antidepressants,[85] and non-steroidal anti-inflammatory drugs,[86] and by non-use of statins;[87] all of these factors are more prevalent among patients with hip fracture than in the background population.[22]

2.5. Literature review

We performed a review of current literature examining the association of hip fracture and stroke and how these conditions impact the prognosis following incident hip fracture. Specifically, we searched for studies addressing the incidence of stroke following hip fracture and risk factors hereof (Study I), risk factors for mortality following hip fracture and previous prediction models of this outcome (Study II), prefracture stroke history as a risk factor for postoperative mortality (Study III), and prefracture stroke history as a risk factor for recurrent fracture (Study IV).

The literature search was performed in MEDLINE (PubMed) for each study separately. Searches were performed using the search builder with the Boolean operators AND/OR, and each search string was employed both with Medical Subject Headings (MeSH) terms and without MeSH terms. The search was restricted to studies published in the past 20 years and was last updated on 14 June 2022. The reference lists of the relevant papers were also screened for other relevant papers that were not identified by the search. The supplementary material, Tables S1-S5, summarizes the studies identified by the searches, whereas the following four sections provide a motivation for each study based on the listed literature.

2.6. Risk of postoperative stroke following hip fracture surgery (Study I)

The cumulative incidence of postoperative stroke among patients with hip fracture is relatively consistently reported to be around 4% – 5% in the first postoperative year (Supplementary Table S1),[11,88-91] with one exception from China reporting a lower incidence of only 1.5%.[92] Incidences appear to be highest in the earliest phase; around 1% for in-hospital stroke risk[21] and around 2% for 30-day stroke risk.[11] Compared with the general population of similar age and sex, these incidences indicate an increased relative risk of 1.5 to 2 during the first year following hip fracture.[11] The previously identified risk factors for postoperative stroke include comorbidity burden and generally accepted risk factors for stroke, including previous stroke, diabetes, heart failure, AF, arterial hypertension, and advancing age.

Evaluation of cardiovascular risk factors is a built-in part of the clinical work at internal medicine and geriatric wards. When assessing the risk of stroke, evaluation of AF history is the first step. If present, the next step is consideration of other risk factors using the CHA_2DS_2-VASc score (Congestive heart failure, hypertension, age ≥75 years , diabetes, previous stroke/transient ischemic attack (TIA)/systemic embolism (2 points), vascular disease, age 65-74 years and female sex).[93-95] In the general population, the presence of AF and a CHA_2DS_2-VASc score equal to or greater than 2 in men and equal to or greater than 3 in women reflect an annual stroke risk of more than 1% and indicate oral anticoagulant treatment (OAC) with either warfarin or direct-acting oral anticoagulants (DOACs) in order to reduce cardioembolic stroke risk.[94,95] If AF is not present, patients are only considered for platelet aggregation inhibitors (commonly named platelet inhibitors), such as low-dose acetylic salicylic acid or clopidogrel - depending on cardiovascular history and risk factors – to reduce the risk of future atherosclerotic events. Although a clear discrepancy in the evaluation of AF and non-AF patients is observed in the clinic, the CHA_2DS_2-VASc score includes risk factors that are also relevant for non-AF patients, and it has been shown to predict cardiovascular events and death among patients with medical conditions other than AF.[96-98]

Considering the elevated stroke risk in patients with hip fracture, a tool to estimate the absolute risk of postoperative stroke using the normal clinical workflow, such as the CHA_2DS_2-VASc score, is needed among all patients with hip fracture, irrespective of AF status, in order to translate previous epidemiologic findings into a clinically useable context. Furthermore, current treatment with antithrombotic agents (i.e., OAC or platelet inhibitors) must be considered in the analysis.

2.7. Prediction of postoperative mortality (Study II)

The risk of postoperative mortality has been extensively studied in patients with hip fracture. Such studies have sought, among others, to identify risk factors for postoperative mortality (Supplementary Table S2). Results from these studies have recently been systematically reviewed.[99,100] The most important risk factors

for a poor outcome are increasing age, male gender, low socio-economic status, institutionalization, high comorbidity level, low Body Mass Index (BMI)/poor nutritional status, low functional status, poor mobility, surgical delay, extracapsular fracture type, and cemented transplants.[71]

Numerous prediction models for mortality have been developed or tested on populations of patients with hip fracture (Supplementary Table S3). All studies perform moderately based on model discrimination, regardless of whether they seek to predict in-hospital, 30-day, or 1-year mortality. A 2015 review co-authored by the developer of the Nottingham Hip Fracture Score (NHFS) found only five models that had been used in three or more studies;[101] the American Society of Anesthesiology score, the Charlson Comorbidity Index (CCI) score, the Estimation of Physiologic Ability and Surgical Stress (E-PASS), the Orthopedic Physiologic and Operative Severity Score for the Enumeration of Mortality and Morbidity (O-POSSUM), and the NHFS. Because the other scores are generic, the review concluded that the NHFS is probably the most suitable prediction model for patients with hip fracture. For planning rehabilitation and relevant preventive strategies for each individual patient with hip fracture, 1-year mortality is a more relevant measure than 30-day mortality. However, the NHFS has primarily been evaluated for prediction of 30-day mortality and it remains sparsely used in the clinical setting outside of the United Kingdom. The developers of the NHFS do not present any internal validation (i.e., test of model performance on own data) for 1-year mortality,[102] but others have tested the model performance on external data (= external validation).[103,104] Since the review from 2015 was published, new models for predicting 1-year mortality in patients with hip fracture have emerged.[104-107] However, only two of these models[105,107] present a proper internal validation in line with the recommended statistical standards.[108] The first study includes similar parameters as the previous models, including the NHFS (age, sex, nursing home residency, admission hemoglobin, cognitive score, and individual comorbidities),[105] whereas the latter only includes age, sex, heart failure, and two functional evaluations (difficulties preparing meals, unable to drive).[107]

None of the previous models include mobility despite its documented association with mortality.[109] Moreover, only a few, selected, comorbidities are included. However, the impact of comorbidities may increase with increasing follow-up time, and including a wider range of comorbidities, or a comorbidity index, may therefore be more productive in terms of predicting 1-year mortality. Finally, the majority of the previous studies are based on a relatively small cohort of patients ($n < 1000$) and have not been externally validated.

In conclusion, previously published models have important limitations. Furthermore, none of them have found their way into everyday clinical practice internationally. To further explore the impact of multiple risk factors on the prognosis following hip fracture surgery, it is necessary to investigate the interplay between the different well-known risk factors, including a broad spectrum of comorbidities, and other important

elements such as mobility and nutrition, thereby capturing more aspects of the frailty syndrome than has been accomplished with previous models. Finally, by visualizing the absolute risk, an increased understanding of how the risk factors increase the mortality risk, independently or in concert, may be obtained alongside enhancing the clinical usefulness of the model.

2.8. Interaction effect of stroke history and hip fracture on postoperative mortality (Study III)

The prevalence of stroke history among patients undergoing hip fracture surgery is reported to be around 15% in a Danish population of patients with hip fracture compared with 10% in an age- and gender-matched comparison cohort from the general population.[22] This is in line with the incidences reported in other studies,[53,110-112] although some studies also report a lower prevalence.[113,114] Whether mortality is increased among patients with hip fracture and a stroke history compared with patients with hip fracture without a stroke history is debatable (Supplementary Table S4).[53,110,111,113-116] Similarly, the impact of a stroke history on patients' functional capabilities after hip fracture rehabilitation is reported inconsistently.[110-113,115,117] Not surprisingly, the prefracture functional level has been demonstrated to influence the prognosis following hip fracture surgery.[99,118]

Previous studies in this field have several limitations that may explain the divergent associations; they are relatively small single-center studies,[53,111,115,116] they were conducted at a time where the prognosis following both conditions was markedly different,[53,113,116] they lack relevant confounder control,[53,114,115] they have applied exclusion criteria that severely influence their external validity,[113,116] or they have inappropriate exposure definitions, including either all neurological diseases[115] or only post-stroke hemiplegia.[114] In addition to an evaluation of the association between prefracture stroke history and mortality, the timing of the association indicating the underlying mechanism driving the association may be of pivotal clinical relevance; such mechanisms may include acute complications in the early postoperative phase, such as infections or new cardiovascular events, which affect short-term mortality; or they may include insufficient rehabilitation that increases the risk of chronic disabilities and thereby impairs the long-term prognosis.

Furthermore, it remains unknown whether a synergistic effect between hip fracture and stroke exists. To reduce mortality, it is essential not only to obtain a better understanding of stroke history as a risk factor but also to elucidate the interaction between stroke history and hip fracture that affects mortality beyond the independent effects of the two conditions.

2.9. Prefracture stroke history and the risk of recurrent fracture (Study IV)

Patients with hip fracture are at increased risk of sustaining recurrent hip fracture or other osteoporotic fractures compared with the background population.[119,120] Based on the studies listed in Supplementary Table S5, the 1-year cumulative incidence of second hip fractures varies from 2% – 9%. This variation may be due to the use of different statistical approaches, different methods for detecting second fractures in the clinical registries, and few outcomes (~50 - 100), resulting in considerable uncertainty. A tendency is observed towards a higher incidence of recurrent fracture in populations from the northern part of Europe, which historically have a high prevalence of osteoporosis.

Several studies have investigated risk factors for recurrent hip fracture, but the risk of type II error is substantial due to the low number of events in many of these studies.[121-126] Consequently, the reported results are diverging, and a 2016 systematic review failed to establish any definite agreement on risk factors for recurrent hip fracture.[127] The review highlights female sex, higher age, poor general health status, impaired vision, stroke, BMI, dementia, and institutionalization as the most often identified risk factors; however, many studies find no association with these factors.[127] In the years following this review, several large cohort studies have been published,[120,128,129] reporting that increasing CCI score, diabetes, and various cardiovascular risk factors are associated with recurrent hip fracture.

Only two studies[129,130] identify stroke history as a risk factor for second fracture, whereas others observe no such association.[124-126,131] This somewhat contrasts the agreement that patients with stroke have an increased risk of incident hip fracture.[57,58,132] Patients with a stroke history more often have impaired prefracture mobility than those without a stroke history[58] and, furthermore, their rehabilitation outcomes are worse.[113] This may increase the risk of recurrent fracture; however, on the other hand, patients with very poor mobility might ambulate less and thereby have reduced risk of falling. No previous studies have accounted for the patients' baseline mobility in their analysis. Another contributing factor, possibly explaining the missing association found in several studies, may be collider bias (explained in section 6.5.2),[133,134] a methodological issue in the study design that has not previously been addressed.

2.10 Knowledge gaps

Risk of postoperative stroke (Study I)

Although the CHA_2DS_2-VASc score has previously been used to predict ischemic stroke and cardiovascular events in non-AF populations, surgical patients with a distinct pro-coagulant profile have never been examined. Thus, a systematic evaluation of cardiovascular risk in patients with hip fracture using the CHA_2DS_2-VASc score could potentially improve our understanding of the risk of ischemic stroke and the thromboembolic risk following hip fracture.

Prediction of postoperative mortality (Study II)

Although several prediction models for 1-year mortality on patients with hip fracture have been developed, only few have been both internally and externally validated, leaving room for local variations to impact the importance of the individual predictors. All previous models encompass only a few selected comorbidities and lack important aspects of the patient frailty syndrome, such as nutrition and mobility status. Furthermore, none of them have been broadly implemented in the clinical workflow internationally

Interaction effect of stroke history and hip fracture (Study III)

Although several studies have been conducted in the field, it remains controversial whether prefracture stroke history impacts the prognosis following hip fracture. Furthermore, none of the previous studies have investigated the possible temporal pattern of the association, which may answer whether the effect of stroke is predominantly seen during short-term or long-term follow-up. Finally, no previous study has investigated an interaction effect of stroke and hip fracture on mortality, which could improve our understanding of how the two conditions affect each other.

Prefracture stroke history and the risk of recurrent fracture (Study IV)

Even though it has been established that stroke is a strong risk factor for incident hip fracture, it is disputed whether the same association applies between stroke and recurrent hip fracture. Previous results could be influenced by effect modification from baseline mobility and by collider bias. Thus, a high-powered study investigating these issues is warranted.

3. Aims and hypothesis

The overall aim of this PhD project was to extend current knowledge of the interplay between hip fracture and stroke, and to put this knowledge into a clinical context.

Risk of postoperative stroke (Study I)

Hypothesis The CHA_2DS_2-VASc score predicts ischemic stroke, thromboembolism, and death equally well among patients with and without AF. The discrimination of the score as a prediction model is moderate.

Aim: To apply the CHA_2DS_2-VASc score on a population of patients with hip fracture – with or without AF – to predict the risk of ischemic stroke, thromboembolism, and mortality up to 1 year after hip fracture surgery.

Prediction of postoperative mortality (Study II)

Hypothesis: By using only information available at the time of admission, we can create a simple and user-friendly risk chart that efficiently predicts 1-year mortality among patients with hip fracture. We expect the absolute mortality risk to vary substantially within the same level of each predictor, based on the level of the other predictors.

Aim: 1) To develop a prediction model for 1-year mortality in patients with hip fracture, using only patient-related information that is present or easily obtainable at the time of admission. 2) To show the interplay between the relevant risk factors through a transparent variable selection process and via an intuitive visualization of the final model. 3) To extend the visualization to serve as a user-friendly risk chart that could be implemented in daily clinical work.

Interaction effect of stroke history and hip fracture (Study III)

Hypothesis: An interaction effect on both the absolute and the relative scale will be observed at all follow-up times, indicating excess mortality among patients with both hip fracture and stroke above what is expected from each individual disease.

Aim: To explore the interaction effect between hip fracture and stroke by investigating postoperative mortality in a cohort of patients with hip fracture with and without stroke, matched with a comparison cohort from the general population with and without stroke at different follow-up times, including 30-days, 1-year, and 5 years after surgery.

Prefracture stroke history and the risk of recurrent fracture (Study IV)

Hypothesis: Patients with incident hip fracture and a prefracture stroke history have an increased risk of recurrent hip fracture. This increased risk is present mainly among patients with poor mobility, whereas

patients with good mobility do not have an increased risk. The effect of collider bias on the association between stroke history and recurrent hip fracture is marginal.

Aim: 1) To investigate the effect of stroke history on the risk of recurrent hip fracture within 2 years in a cohort of patients with incident hip fracture, and to include possible effect modification from baseline mobility in the analysis. 2) To investigate the extent of collider bias in this association.

4

4. Methods

The following sections describe the methods used for Study I-IV. An overview of methodology for each study can be found in Table 1.

4.1. Setting

The Danish healthcare system is predominantly tax supported. This implies that citizens incur no expenses for visits at the general practitioner or for any hospital and emergency treatment, including all hip fracture and stroke treatment which is performed at public hospitals; and that they receive part reimbursement of prescription medicine from community pharmacies.[135]

4.2. Data sources

Denmark (population approximately 5.8 million in 2022) has a longstanding tradition for running high-quality, population-based nationwide medical and administrative databases. Although these databases were not originally developed for the purpose of research, they represent a unique source of detailed individual-level data. The databases can be linked through the unique 10-digit personal identifier assigned to each person upon birth or immigration. This identifier, the CPR number, is used in all administrative and medical databases and encodes the date of birth, a four-digit code that makes it possible to distinguish persons born on the same date, and furthermore, the last digit indicate the sex of the person (odd for males and even for females).[136]

As an important supplement to the administrative registries, the five regions in Denmark fund the clinical quality databases under *The Danish Clinical Quality Program – National Clinical Registries* (RKKP).[137] Currently hosting 85 clinical quality registries, the RKKP has the primary goal of monitoring and improving the quality of care. The registries in the RKKP typically cover all patients treated for a specific condition and are also accessible for research purposes. They provide the possibility to obtain important information that is not routinely recorded for all hospital contacts through the administrative registries.

All studies in this thesis were based on prospectively collected data from the national registries; the following section gives a short presentation of these registries.

4.2.1. Administrative and medical databases

The Danish Civil Registration System[136] was initiated in 1968. With daily updates since 1989, this system holds information on vital status and migration, thus ensuring complete follow-up of all individuals. We used information on age and sex (through the CPR number) and vital status for the outcome of all-cause mortality.

The Danish National Patient Registry (NPR)[138] holds information on non-psychiatric hospitalizations since 1977 and was upgraded in 1995 to also include psychiatric hospitalizations and outpatient and emergency department contacts. For each contact, one primary and up to 20 secondary diagnoses are recorded. For the period relevant for this thesis, all contacts are coded using the International Classification of Diseases – 10th edition. We used the NPR to obtain information on exposure and potential confounders in all studies; and in Study I and IV, the outcome was also derived from NPR data.

The Danish Multidisciplinary Hip Fracture Registry (DMHFR).[32] This clinical quality registry, established in 2003, holds information on all patients aged 65 years or older who are registered at Danish hospitals and who fulfill the following criteria: 1) A primary diagnosis of hip fracture (DS720 - DS722), 2) A sub-code indicating the side of the fracture, 3) A surgical procedure code corresponding to a hip fracture operation (Nordic Medico-Statistical Committee classification:[139] KNFB* or KNFJ4* - 9*) coded during the admission. Reporting to the registry is mandatory and has been so since 2006; and since 2010, the registry has been capturing data directly from the NPR. All four studies used this registry to define the study population and, furthermore, data on other relevant variables, such as BMI and mobility, were also obtained.

The Danish Stroke Registry[52] is a clinical quality registry established in 2003 that holds information on all adults aged 18 or more admitted to Danish hospitals with acute stroke (ischemic, intracerebral hemorrhage, unspecified). TIA was added in 2013 and subarachnoid hemorrhage in 2017. In Study III and IV, this register was used for sensitivity analysis as an alternative way to define stroke exposure and, furthermore, the severity of strokes was assessed using the Scandinavian Stroke Scale score[140] which is routinely recorded in the registry.

The Danish National Prescription Registry[141] records all prescription medicine dispensed by community pharmacies in Denmark. The date of purchase and the type of medication (Anatomical Therapeutic Chemical classification codes) can be retrieved as can the product number, enabling the possibility to obtain information on dose and package size. Baseline use of relevant prescription medicine was assessed in Study I, III, and IV.

Statistics Denmark. The publicly available 'StatBank Denmark'[142] was used to compute the overall mortality of the background population in Study II.

4.3. Study designs and study populations

All studies in this thesis are nationwide cohort studies based on the DMHFR. The study period varied between the four studies based on data availability (BMI and mobility were not recorded before 2011), the frequency of the outcome of interest, and duration of the follow-up period.

In Study III, we used a matched cohort design. The matching population was obtained by drawing a random sample of the entire Danish population (from the CRS linked with NPR data): For each patient with hip fracture, 10 individuals were sampled with similar age, sex, and stroke status but free of hip fracture. Matching was done with replacement as this has proven to be the most robust method when the outcome is frequent.[143]

Table 1: Summary of materials and methods

	Study I	Study II	Study III	Study IV
Objectives	Evaluate the risk of ischemic stroke, any thromboembolism, and death among patients undergoing hip fracture surgery	To develop a user-friendly prediction model for 1-year mortality among patients undergoing hip fracture surgery	To evaluate the impact of previous stroke on the postoperative mortality risk following hip fracture.	To evaluate the effect of previous stroke on the risk of second fracture among patients with incident hip fracture
Setting	Danish hospitals, Dec 2003 – Nov 2016 Follow-up end: June 2017	Danish hospitals, Jan 2011 – Dec 2017 Follow-up end: Dec 2018	Denmark, Jan 2010 – Dec 2018 Follow-up end: Dec 2018	Danish hospitals, Jan 2011 – Dec 2018 Follow-up end: Dec 2018
Design	Nationwide cohort study	Nationwide cohort study	Nationwide cohort study	Nationwide cohort study
Data sources	CRS, NPR, DMHFR, prescription registry	CRS, NPR, DMHFR, StatBank Denmark	CRS, NPR, DMHFR, DSR, prescription registry	CRS, NPR, DMHFR, DSR, prescription registry
Study population	N = 78,096 patients with incident hip fracture, divided according to AF history at baseline: AF cohort (N = 12,319) and non-AF cohort (65,777)	N = 28,791 patients with incident hip fracture. Random split into a development cohort (70%) and validation cohort (30%)	Hip fracture cohorts: N = 53,430 (8,433 with previous stroke). Comparison cohorts: 534,292 (84,330 with previous stroke)	N = 48,230 patients with incident hip fracture, divided according to stroke history at baseline: Non-stroke cohort (N = 44,102) and stroke cohort (4,128)
Matching	-	-	Age, sex, stroke history (with replacement)	-
Exposure	CHA_2DS_2-VASc score	Baseline predictors: Age, sex, CCI score, HFR score, AF, BMI, CAS, nursing home residency	Hip fracture and stroke. Stratification on age and CCI	Prefracture stroke (5 years lookback) Stratification on mobility status
Outcome	Ischemic stroke, any thromboembolism (arterial or venous), all-cause mortality	All-cause mortality (1-year)	All-cause mortality (0-30 days, 31-365 days, 1-5 years)	Second hip fracture (primary) and major osteoporotic fracture
Covariates	Year of diagnosis, BMI, redeemed prescription of OAC or PI 90 days before fracture	-	Age, sex, CCI score	Age, sex, CCI score, AF, BMI
Statistical analysis	Cumulative incidence (competing risk of death), Cox regression, discrimination	Decision tree modeling, logistic regression (final model), discrimination (AUROC), calibration	Standardized MR, cumulative incidence, Cox regression, interaction contrast (of MRs), attributable proportion (of HRs)	Cumulative incidence (competing risk of death), Cox regression

	Study I	Study II	Study III	Study IV
Sensitivity analyses	1. Exclusion of patients on OAC 90 days before fracture 2. Censoring of patients if diagnosed with AF during follow-up	1. Multiple imputation of missing values (BMI, CAS, type of residence) 2. Split sample validation based on a) calendar year and b) geography instead of random split 3. Bootstrap validation instead of split sample validation 4. a) exclusion of dementia in the CCI score and b) exclusion from the CCI score and including dementia as an independent predictor	1) Stratified analyses on stroke severity categories 2) Stratified analyses on stroke more or less than 6 months before fracture 3) Stratified analyses based on stroke type (ischemic or hemorrhagic)	1) Stratified analysis on shorter stroke lookback (2 years) and on stroke severity 2) Multiple imputation of missing values (BMI, CAS) 3) Adjusting for known and possibly confounding variables due to collider bias

Abbreviations: AF: Atrial fibrillation, BMI: Body Mass Index, CAS: Cumulated ambulation score, CCI: Charlson Comorbidity Index, CHA_2DS_2-VASc: mnemonic for evaluation of stroke risk (Congestive heart failure, hypertension, age ≥75 years , diabetes, previous stroke/TIA/systemic embolism (2 points), vascular disease, age 65-74 years and female sex), CRS: Civil Registration System, DMHFR: Danish Multidisciplinary Hip Fracture Registry, DSR: Danish Stroke Registry, HFR: Hospital frailty risk, HR: Hazard ratio, NPR: National Patient Registry, OAC: Oral anticoagulant, PI: Platelet inhibitor.

4.4. Exposures

4.4.1. AF and CHA_2DS_2-VASc score (Study I)

From the NPR, we identified any AF diagnosis and CHA_2DS_2-VASc comorbidities prior to admission for hip fracture (Appendix I, Supplementary Table S1). As an exception, due to expected low completeness of the diagnosis of hypertension in the NPR, patients were categorized as having hypertension if they had the relevant diagnosis from the NPR or had redeemed a minimum of two different antihypertensive medications before sustaining hip fracture. The score was computed for each patient according to the algorithm;[94] a sum of points for congestive heart failure, hypertension, diabetes, vascular disease, age 65-74 years, and female sex (1 point each) and age ≥75 and previous stroke/TIA/systemic embolism (2 points each).

4.4.2. Candidate predictors for the prediction model (Study II)

In Study II, we searched for predictors that were either available in the electronic patient record at the time of admission or easy to obtain through, e.g., the routine admission interview or examination. Furthermore, the candidate predictors were required to have a known association with postfracture mortality. Based on these criteria, we identified the following:

1) Based on the NPR, we computed the CCI score[144] and the Hospital Frailty Risk score.[145]
2) The diagnosis of AF was obtained from the NPR.
3) Information on fracture type and BMI was extracted from the DMHFR.
4) The Cumulated Ambulation Score (CAS), a simple mobility score[146] indicating patient prefracture basic mobility, was obtained from the DMHFR. This score ranges from 0 (completely immobile) to

6 (fully mobile). The prefracture value is based on information from the patient and relatives on the following activities: A) getting in and out of bed, B) sit-to-stand from a chair with armrests, and C) indoor walking. Each domain is given a score of 0 (incapable, despite human assistance), 1 (capable, with human assistance), or 2 (capable, independently).

5) Nursing home residency at the time of admission; information was found in the DMHFR.
6) Information on age and sex was obtained from the CPR number.

See Appendix II, Supplementary Table S1A+B for all coding algorithms.

4.4.3. Prefracture stroke history (Study III and IV)

A diagnosis of ischemic (I63), hemorrhagic (I60-I62), or unspecified type stroke (I64) from the NPR before the hip fracture admission date classified the patients as having a prefracture stroke history. In both studies, the main analysis was conducted without distinguishing between these subtypes. In contrast, a sensitivity analysis was performed in Study III, dividing patients according to the type of (the last recorded) stroke. In Study III, we used a lookback period of 15 years, whereas this period was only 5 years in Study IV. This discrepancy was due to differences in the study question and different theories regarding the biological mechanisms by which stroke impacted the prognosis. However, in both studies, we did sensitivity analyses restricting the exposure period to shorter intervals. The impact of stroke also varies substantially between individuals according to its size and anatomical location, which influence the sequelae and ensuing neurological deficits. As a proxy for this variation, we used the Scandinavian Stroke Scale score to estimate stroke severity.[140,147] This tool is used routinely in the acute phase of stroke care in Denmark and scores patients according to nine possible neurological deficits: Consciousness, eye movement, arm motor power, hand motor power, leg motor power, orientation, speech, facial palsy, and gait. The score ranges from 0 to 58 points. We used the categorization employed by the Danish Stroke Registry grouping patients into severe (≤ 29 points), moderate (30-44 points), or mild (≥45 points) stroke.

4.5. Outcomes

Follow-up was initiated on the day of operation in Study I – III, whereas the discharge date was used as the starting point of follow-up in Study IV. In Study I and II, patients were followed for 1 year, whereas Study III and IV had several distinct follow-up time points: 30 days and 1 and 5 years in Study III and 1 and 2 years in Study IV.

4.5.1. Mortality (all studies)

All-cause mortality was used in all studies as main outcome (Study II and III), secondary outcome (Study I), or as a competing event (Study I and IV). In all instances, information on all-cause mortality was obtained from the Civil Registration System, which reports the exact date of death.

4.5.2. Ischemic stroke and any thromboembolism (Study I)

Ischemic stroke during follow-up was identified through the NPR. We used a somewhat broader definition of ischemic stroke in this study, including unspecified strokes and the TIAs in the outcome. (Appendix I, Supplementary Table S1). As both AF and the CHA_2DS_2-VASc score were expected to increase the risk of other cardiovascular events than ischemic stroke, we included a composite endpoint of any thromboembolism. This category also included myocardial infarction and other peripheral arterial embolic events and venous thromboembolisms, including pulmonary embolism.

4.5.3. Recurrent hip fracture and major osteoporotic fractures (Study IV)

Patients were followed for 2 years from the day of discharge. To avoid identifying a re-coding of the original hip fracture as an outcome, the second hip fracture was identified in the NPR as specified in previously published papers on this topic, using Danish data:[119,128] Following discharge of patients with incident hip fracture, all new hip fracture diagnoses registered during an emergency admission were regarded as recurrent hip fractures. However, if the same type of fracture was diagnosed on the same side within the first 6 months of follow-up, it was regarded as a duplicate diagnosis and was therefore discarded. The secondary outcome of major osteoporotic fractures was a composite outcome that included hip fracture (identified as for the primary outcome), fractures of the proximal humerus, distal forearm fractures, and vertebral fractures (Appendix IV, Supplementary Table 1).

4.6. Covariates

We retrieved information on other variables that characterized the study population at the index hip fracture. We constructed directed acyclic graphs (DAGs) in Study I, III, and IV to evaluate which variables were relevant for adjustment in the analyses (Figure 3A-C). Using the DAGs and our subject knowledge, we evaluated how these variables could possibly bias the investigated associations and categorized them as either effect modifiers (variables altering the exposure-outcome association within categories of the variable), confounders (factors associated with both the exposure and the outcome, while not a part of the causal pathway), or competing risks (events occurring during follow-up that alter the risk of having the outcome). As Study II was a prediction study, it did not include covariates *per se* as all factors relevant for the association were included as predictors in the prediction model. Table 2 summarizes the use of relevant covariates in all studies.

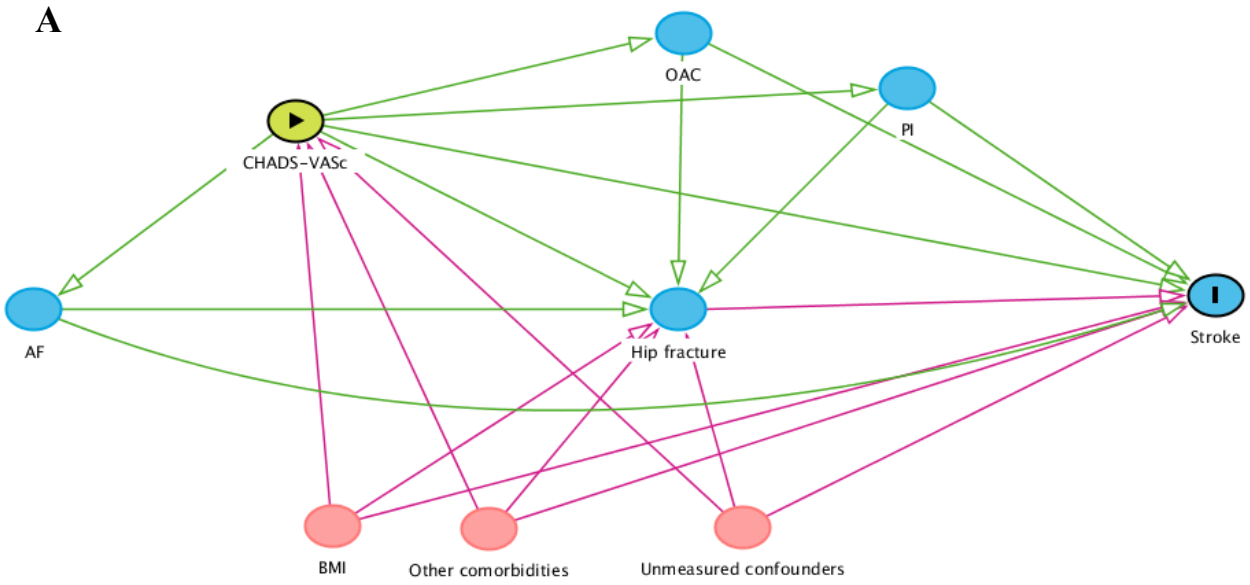
Table 2. Schematic overview of covariates included in the studies

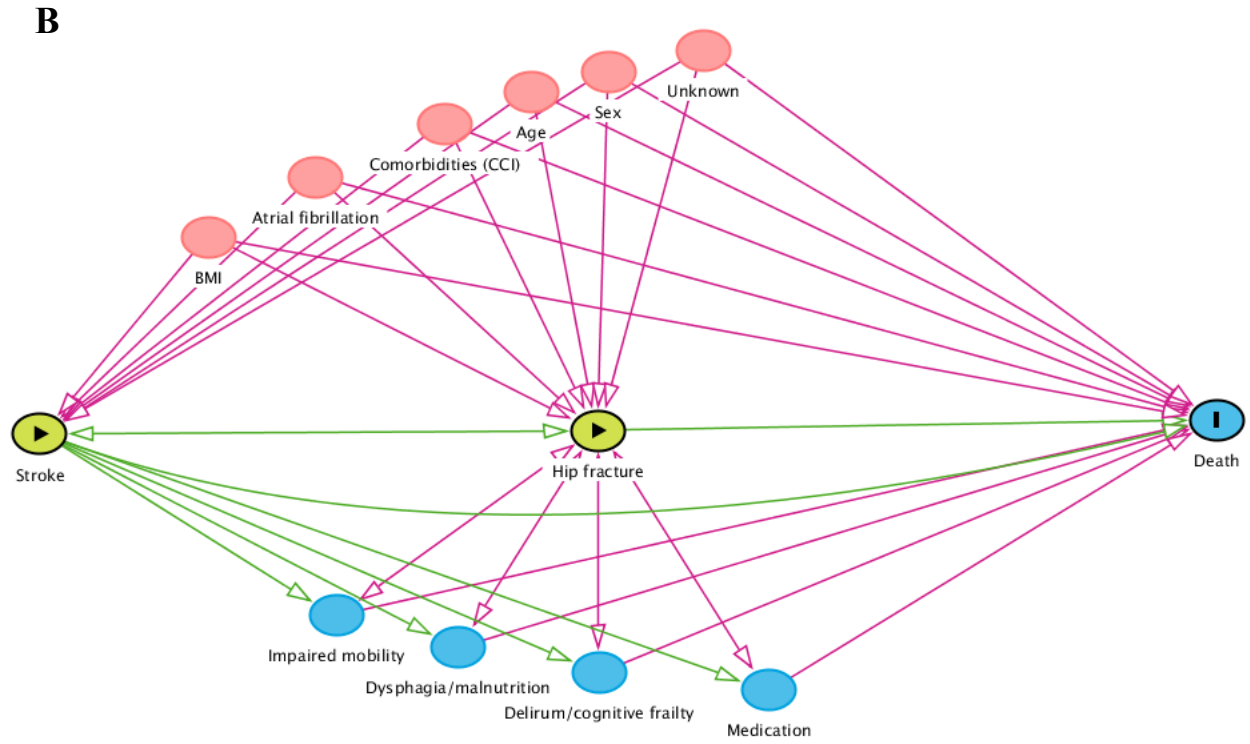
	Study I	Study III	Study IV	Data source
Included as effect modifier (Stratified on)				
Atrial fibrillation	✓			NPR
Age		✓		CRS
Charlson Comorbidity Index score categories		✓		NPR
Cumulated Ambulation Score			✓	DMHFR
Stroke severity		✓	✓	Danish Stroke Registry
Stroke lookback period		✓	✓	NPR
Stroke type		✓		NPR
Included as confounder (adjusted for)				
Age		✓	✓	CRS
Sex		✓	✓	CRS
Charlson Comorbidity Index score		✓	✓	NPR
Body Mass Index	✓		✓	DMHFR
Year of diagnosis	✓			DMHFR
OAC/PI	✓			Prescription registry
Baseline medication use		✓		Prescription registry
Atrial fibrillation			✓	NPR
Other factors associated with fractures, but not stroke*			✓	NPR, Prescription registry
Included as censoring variables or competing risks				
Atrial fibrillation	✓			NPR
OAC/PI	✓			Prescription registry
Death	✓		✓	CRS

Abbreviations: CRS: Civil Registration System, DMHFR: Danish Multidisciplinary Hip Fracture Registry, NPR: National Patient Registry, OAC: Oral anticoagulant, PI: Platelet inhibitor
** These factors include: impaired vision, diagnoses of vertigo or diseases affecting vestibular function, diseases affecting bone mineral metabolism, prefracture osteoporosis treatment, and prefracture treatment with drugs associated with low bone mineral density or increased risk of falling*

The CCI score was used as a proxy for patient comorbidity in all studies. However, we also included other independent comorbidities found to be relevant for the association investigated in Study II-IV. The CCI was developed by Dr. Mary Charlson and colleagues in 1987. It was originally devised as a method for predicting mortality risk in a cohort of 559 acutely admitted medical patients.[144] It comprises 19 distinct disease categories that are weighted from 1-6 points according to the strength of the association. Although an update of the Index, including a new weighting, has been published,[148] it has not proven superior to the original weighting, and all studies in this thesis therefore use the original weights. For adjustment in regression

analyses, we used the CCI as a continuous variable, whereas a categorized version of the CCI (0, 1, 2 or 3+ points) was used for standardization of mortality rates (MRs) and for stratifications (Study III)





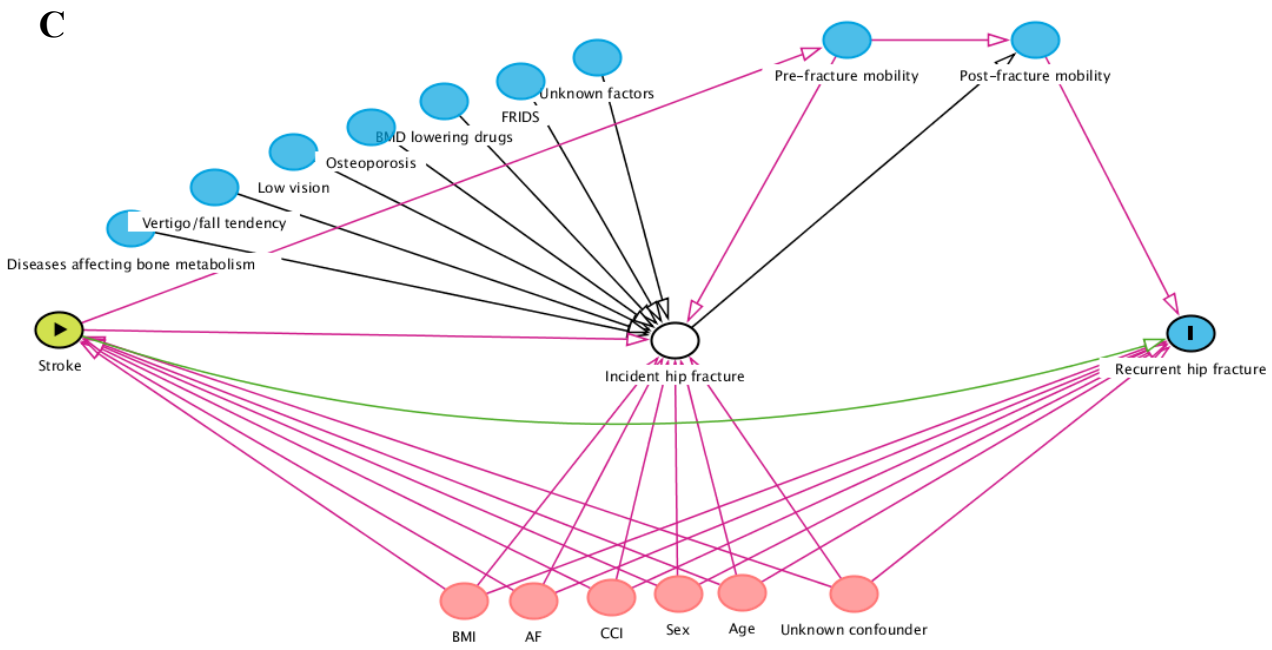


***Figure 3**. Directed Acyclic Graphs (DAGs) of Study I (Panel A), III (Panel B), and IV (Panel C). Abbreviations: AF: Atrial fibrillation, BMD: Bone mineral density, BMI: Body Mass Index, CCI: Charlson Comorbidity Index, FRIDS: Fall-risk-increasing drugs, OAC: Oral anticoagulants, PI: Platelet inhibitors. Illustrated using DAGitty v 3.0 at http://www.dagitty.net*

4.7. Statistical analyses

A summary of the statistical methods applied in each study can be found in Table 1. All statistical analyses for Study II-IV were performed on the remote servers of Statistics Denmark, using the R statistical software version 4.1.3 (The R Foundation for Statistical Computing, www.R-project.org). Analyses for Study I were made on a local dataset using the same software.

4.7.1 Incidence rates (Study I and III)

IRs or MRs describe the number of events occurring during a given period of time – expressed in PYs.[149] In Study I, we describe the IR of all outcomes as an average over the first year of follow-up; however, because of competing risk of death (see next section), this analysis is supplied only as supplementary information. In Study III, MRs are reported as a part of the main analysis and they are also used to inform the interaction analysis on the additive scale (see section 4.7.7). In Study III, the follow-up times were divided into short (0-30 days), intermediate (31-365 days) and long (1-5 years) follow-up, and the MRs were averaged for each time period. In Study III, MRs are standardized to age, sex, and CCI score categories using a direct standardization approach, which allows for a direct comparison of the MRs in the different cohorts despite a different distribution of the covariates.[149] Confidence intervals (CIs) for the rate are calculated on the log scale using the delta method.[149] IRs and MRs were computed using the "popEpi" package for R.[150]

4.7.2 Competing risk of death and cumulative incidence (Study I and IV)

In Study I, the primary endpoint was ischemic stroke; in Study IV, recurrent hip fracture. When dealing with such non-fatal outcomes, the competing risk of death must be considered. Standard survival curves using the Kaplan-Meier method assume non-informative censoring, meaning that patients leaving the study continue to have the same risk of the outcome. Consequently, this method tends to overestimate the risk of the event of interest because patients who die are censored and therefore not counted in the population at risk.[151-153] Naturally, patients cannot sustain either stroke or hip fracture when they are dead. The cumulative incidence function considers such competing risks, and estimates the probability of experiencing the event of interest before the occurrence of a competing event.[153] 95% CIs were estimated using a log-normal approximation.[149] All competing risk analyses were performed using the "cmprsk" package for R.[154]

4.7.3 Cox proportional hazards regression (Study I, III, and IV)

Time-to-event regression analysis was performed in Study I, III, and IV using the Cox proportional hazards regression to obtain covariate-adjusted hazard ratios (HRs) as a relative measure of association. This method compares the hazard rate of events at any given time among the exposure groups and provides a ratio between unexposed and exposed persons still at risk of getting the event. The assumption of proportional hazards was checked using log(-log) plots and found to hold for all studies. The interpretation of the HR is not straight forward and should not be translated directly into relative risk.[155] However, if the probability of the event is low, the HR approximates the relative risk.[155] The interpretation of the HR in the presence of competing risk will be discussed in section 6.5.3. Cox regression analyses were performed using the "survival" package for R.[156]

4.7.4 Decision tree modeling and variable importance (Study II)

The prediction model developed in Study II used a decision tree model technique to inform the variable selection process. Our study question addressed a classification problem (i.e., a binary outcome. Death within 1 year: yes/no) and in this case, the splits in the tree were based on the Gini index, which is a purity measure commonly used when dealing with classification trees.[157] Binary splits are made on the variable that reduces Gini index the most. New splits are performed subsequently until all individuals in each of the sub-cohorts have the same classification or a manually defined stopping criterion is reached (e.g., max number of splits or minimum sub-cohort size). We used 10-fold cross validation to produce and test a series of decision trees using different number of allowed splits and different penalties depending on tree size (cost-complexity).[157] Based on these parameters we were able to choose the model with the best predictive performance and use this to construct a variable importance plot. This plot was constructed by summing the total reduction in Gini index by each parameter in the model and plotting them relative to each other.[158] Thus, the plot is on a relative scale where the parameter contributing the most in the model is set to 100. All

decision tree models were build using the "Tidymodels" framework[159] and the "RPART" package in R,[160] whereas variable importance was constructed with the "VIP" package for R.[158]

4.7.5 Logistic regression (Study II)

We used logistic regression for the development of the final prediction model in Study II. This is the most commonly used regression method when dealing with a binary outcome.[149] This type of analysis was more relevant than a time-to-event analysis such as the Cox regression because the aim of the study was to predict death within 1 year, however we were not interested in the time frame within that first year. Furthermore, when interpreting the model discrimination (see next section) the interpretation is different when validating a Cox model, because the timing of the event is included in the prediction. The logistic regression model produced odds ratios (ORs) with 95% CIs that were subsequently used to predict the absolute risk of 1-year mortality.

4.7.6 Internal validation of a prediction model (Study II)

For internal validation of prediction models, it is recommended to use either split sample or re-sampling techniques.[108] The main analysis was performed using a random split sample technique in which 70% of the cohort was used for model development and the remaining 30% was used for validation. To further test the robustness of our results, we also included sensitivity analyses where the model was developed and validated on a geographical and a temporal split of the dataset. Finally, we performed a bootstrap validation as a sensitivity analysis to include a re-sampling technique for internal validation. Bootstrap refers to a random sampling from the entire cohort (with replacement) on which the model is developed and, subsequently, the model is validated on the entire cohort. This process is repeated several times (30,000 in this case) to ensure stable estimates. This technique can also be used to estimate and adjust for optimism.[108] Many different estimates for predictive performance exist. The most widely used estimates are discrimination and calibration.

Discrimination can be interpreted as the probability that the model affords a patient *with* the outcome a higher risk than a randomly selected patient *without* the outcome.[108] It is estimated as the area under the receiver-operating characteristics (AUROC) curve, which plots 1-specificity (false positive fraction) against the sensitivity (true positive fraction).[149] The ideal prediction model classifies all individuals correctly and would yield a sensitivity of 1, while 1-specificity remains at 0. This situation would produce an AUROC of 1. Contrary to this, completely uninformed guessing of the outcome would statistically be correct in 50% of cases, which would result in an AUROC of 0.5. ROC curves and AUROC estimation were performed using the "plotROC" package for R.[161]

Calibration describes how well the predictions of the model fit the actually observed events. Thus, if 10% of the population can be observed to have the event during follow-up, the model should preferably predict an

overall risk of approximately 10%.[162] Calibration was estimated by plotting the predicted versus the observed risk of the outcome averaged in deciles of the validation cohort. A perfectly calibrated model would produce a diagonal line, whereas a line deviating above the diagonal tends to underestimate the risk and deviation below the diagonal represents an overestimation. This is also indicated by the calibration slope which is the slope of the linear fit of the ten points. The intercept of the linear fit can be used to recalibrate the model if necessary. Visual inspection is considered important in the evaluation of calibration.[108]

4.7.7 Measures of interaction (Study III)

Interaction analysis can be used to break down the joint effect of two exposures on the outcome of interest into the effect of each individual exposure.[163,164] In the present study, we obtained information on the part of mortality that could be attributed to stroke, the part that could be attributed to hip fracture, and the part (if any) that could be attributed to interaction between the two diseases. Thus, we achieved an estimate of the excess mortality among double-exposed patients. It is recommended to present interaction on both the additive and the multiplicative scale.[163,165] We therefore presented the *interaction contrast* based on the MRs to estimate the additive interaction and the *attributable proportion* based on the Cox regression to estimate the multiplicative interaction (Appendix III).

4.7.8 Multiple imputation by chained equations (MICE) (Study II and IV)

Information on type of residence before admission, CAS, or BMI was missing in 15% – 20% of cases. In both studies, the MICE analyses were performed on the assumption that data are *missing at random* – that is, the missing data are dependent on other, observed, variables.[166,167] The MICE technique employs a regression model to estimate the value of the missing data points and, subsequently, the desired analysis can be run on the complete (imputed) dataset. This operation is repeated several times, in which the desired analysis is performed on each imputed dataset. Subsequently, the values are pooled to give one final estimate with 95% CIs also accounting for the in-between variation of the estimates from each imputed dataset. All imputations were performed using the MICE package in R,[168] which also includes tools to graphically inspect the quality of the imputations. Missing data are also discussed in section 6.5.2.

4.8. Ethical considerations

The study was reported to the Danish Data Protection Agency through registration at Aarhus University (record number: AU-2016-051-000001, sequential number 880). Non-interventional registry-based research projects that do not involve human biological material and are based on pure data such as numbers require no notification to the Danish Scientific Ethics Committee.[169]

5

5. Results

The main results of the four studies are outlined in the following. For a detailed description of the results of each study, please see Appendix I – IV.

5.1. Risk of postoperative stroke (Study I)

The final study population counted 78,096 patients undergoing hip fracture surgery from 2004 to 2017. The cohort was stratified according to AF history, which was present in 12,319 (15.8%) individuals. In the AF group, 31.7% of the patients received OAC treatment at the time of hip fracture. Detailed baseline characteristics of the overall cohort and the AF and non-AF cohorts can be found in Appendix I.

The 1-year cumulative incidence of ischemic stroke increased for each increase in CHA_2DS_2-VASc score above 3 in both patients with AF and patients without AF (Figure 4A-B). Patients with a score of 1 to 3 had the same cumulative incidence of 1.5% – 2% (both groups). The highest incidence of 8.6% was found in patients with AF with a CHA_2DS_2-VASc score above 5. The dose-response-like association was also observed for any thromboembolism, where an even better contrast between the categories was seen (Figure 4C-D). Again, the absolute numbers were comparable among patients with AF and patients without AF. Cumulative mortality was substantially lower for patients with a CHA_2DS_2-VASc score of 1, whereas all patients with a score of 2 or higher had a 1-year mortality between 37.6% – 42.2% for patients with AF and 24.7% – 31.8% for patients without AF (Figure 4 (E-F).

The cause-specific HR based on Cox regression using a CHA_2DS_2-VASc score of 1 as a reference showed the same pattern as the cumulative incidences (Appendix I) for all outcomes. Discrimination of the Cox models was moderate to poor, depending on the outcome: 0.63-0.67 for ischemic stroke, 0.6-0.63 for any thromboembolism, and 0.52-0.56 for mortality.

In the sensitivity analysis, excluding patients on OAC at baseline and censoring patients having an incident diagnosis of AF during follow-up changed the results only marginally.

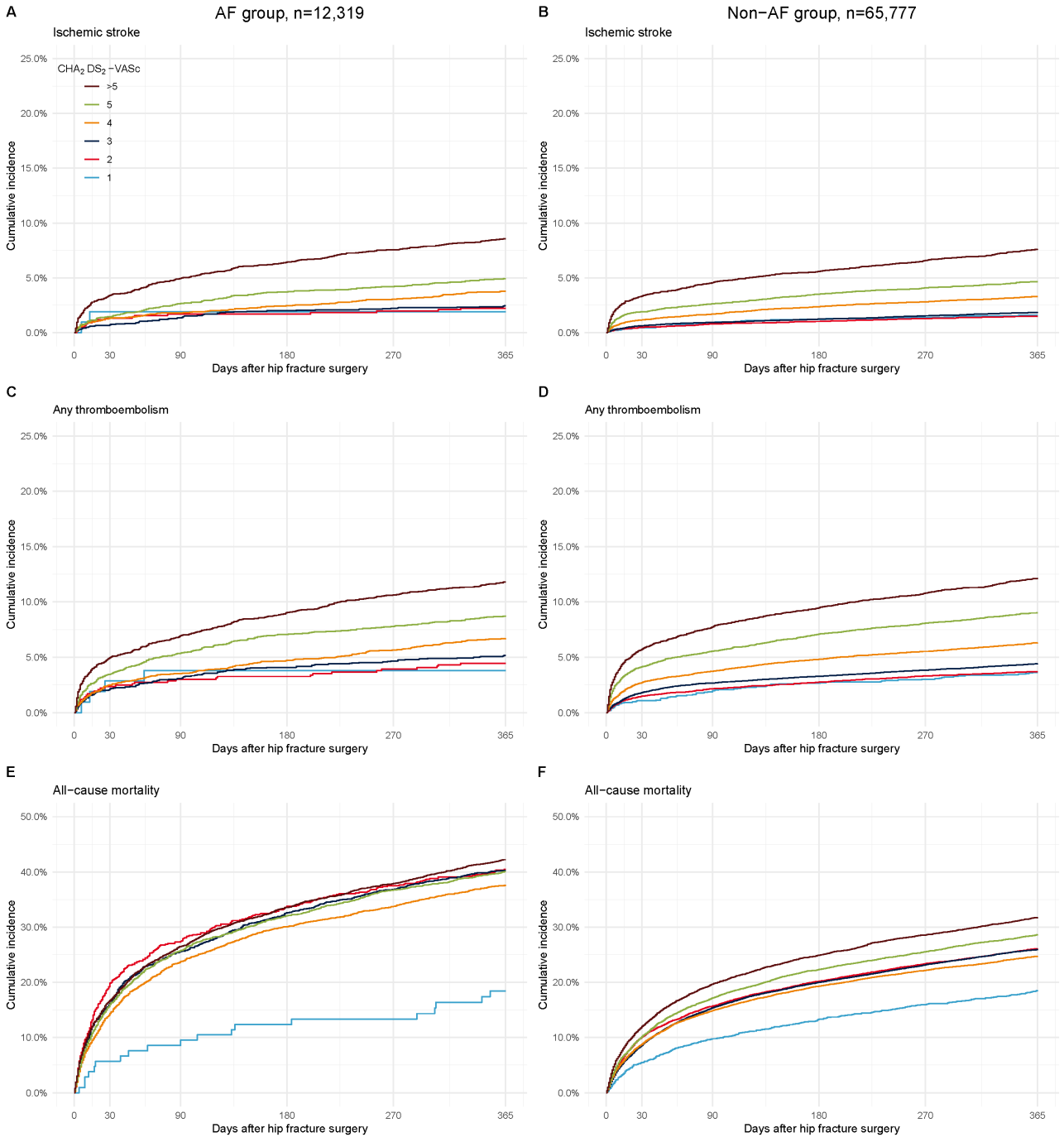


Figure 4. *1-year cumulative incidence of ischemic stroke, any thromboembolism, and death following hip fracture surgery. Patients with atrial fibrillation history (left column) and patients without atrial fibrillation history (right column). Colors indicate CHA_2DS_2-VASc score. Note varying Y-axis scale for fatal and non-fatal outcomes. Figure from Hjelholt TJ, Johnsen SP, Brynningsen PK, Pedersen AB. Association of CHA2 DS2 -VASc Score with Stroke, Thromboembolism, and Death in Hip Fracture Patients Journal of the American Geriatrics Society. Volume 68, 8, 2020, s. 1698-1705. DOI: 10.1111/jgs.16452, Appendix I*[170].

5.2. Prediction of postoperative mortality (Study II)

The final study population included 28,791 patients undergoing hip fracture surgery between 2011 and 2018. Please see Appendix II for a detailed description of the study population, both overall and divided according to patients with/without a fatal outcome within the first year.

All candidate predictors showed a clear dose-response association with mortality (Appendix II, supplementary material) reflected by absolute numbers (cumulative mortality) and relative estimates (univariate logistic regression). The variable importance plot can be seen in Figure 5.

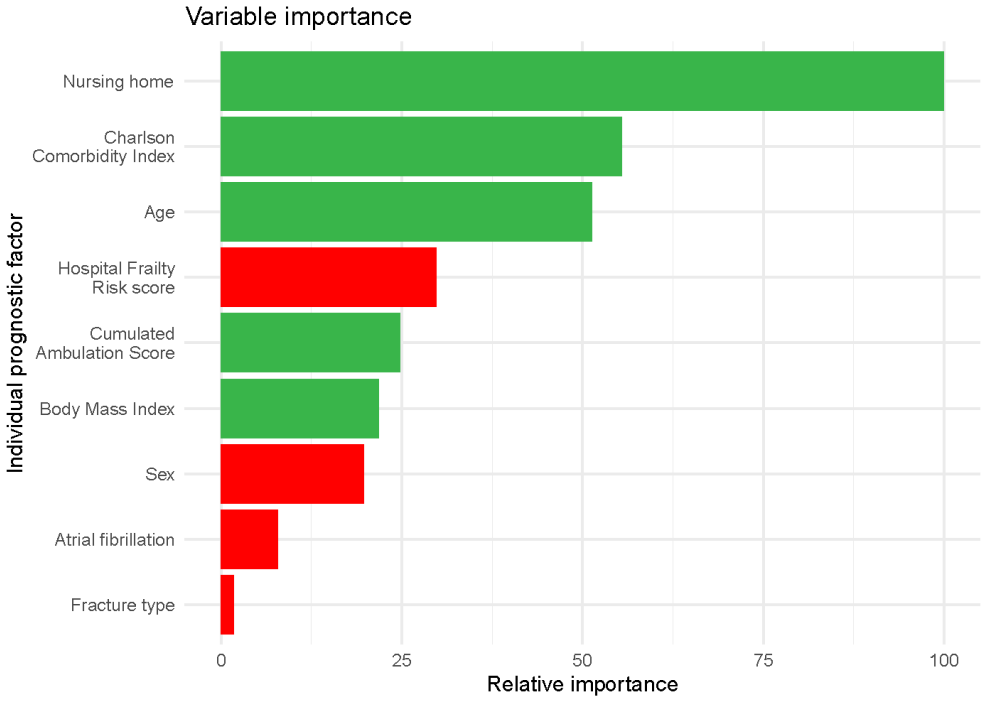
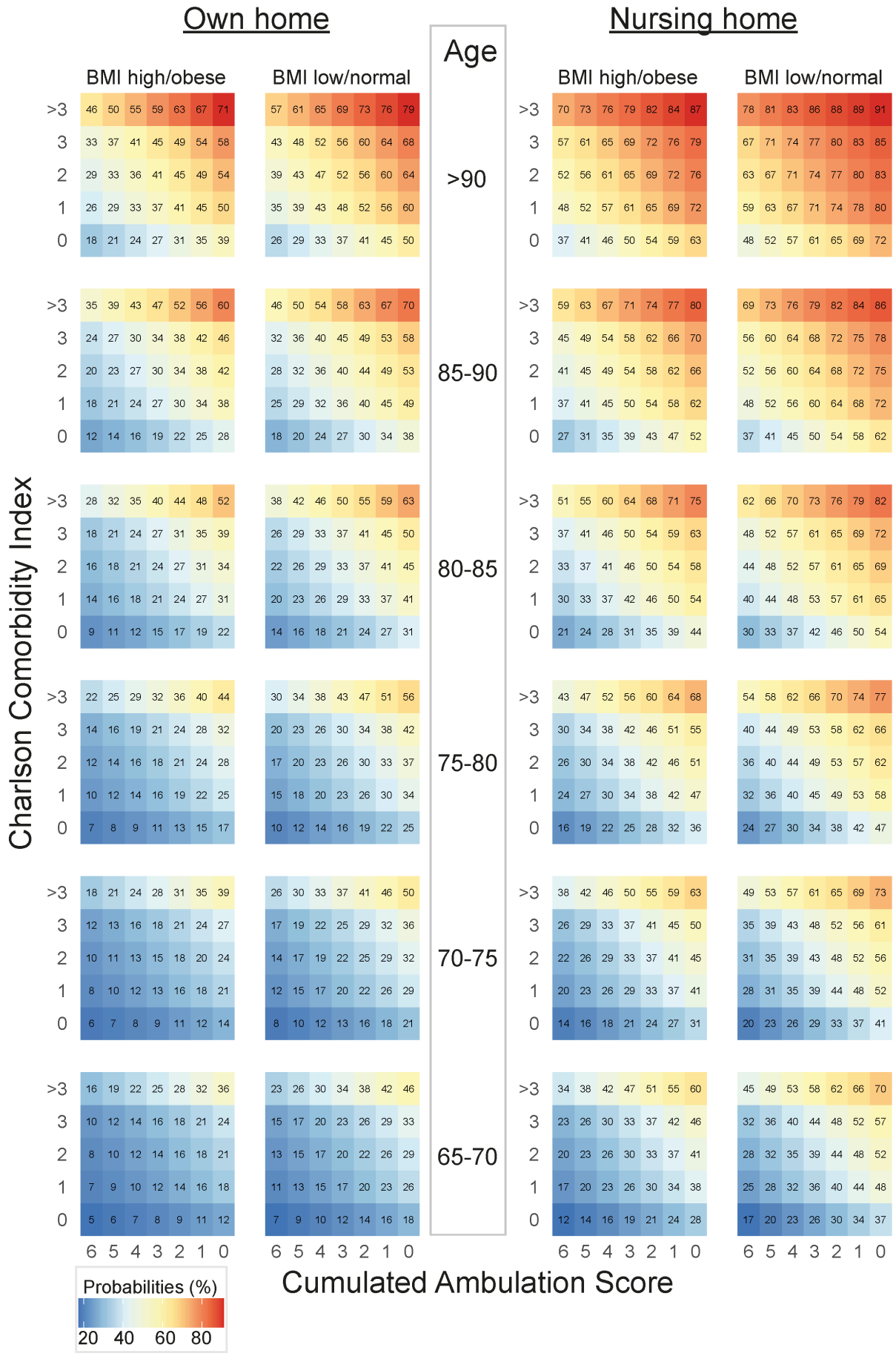


Figure 5. *Variable importance plot showing the relative contribution of each predictor to the decision tree splits. The green variables were selected for the final model. Modified from Hjelholt TJ, Johnsen SP, Knudsen JS, Prieto-Alhambra D, Pedersen AB. Development and validation of a model for predicting mortality in patients with hip fracture. Age and Ageing. 2022;51. DOI:10.1093/ageing/afab233, Appendix II*[118].

The variable selection was based on the following criteria: 1) Only the CCI or the Hospital Frailty Risk score was included due to considerable overlap in diagnoses. Based on Figure 5, the Hospital Frailty Risk was discarded. 2) Stepwise exclusion of predictors below the 25-percentile and reevaluation of model discrimination. Omission of AF, fracture type, and sex resulted in a reduction of the AUROC below 0.005, and these variables were therefore removed. Consequently, the final model included the following predictors: Admitted from nursing home (yes/no), CCI score (categorized into 0, 1, 2, 3, >3), age (categorized in 5-year intervals), CAS (continuous 0-6 points), and BMI (dichotomized into underweight/normal weight and overweight/obese). The final logistic regression model predicted the absolute risk of dying within 1 year following hip fracture surgery (Figure 6). Based on the predictions, mortality ranged from 5% to 91%, depending on the combination of predictors. Furthermore, the variation in estimated mortality also varied greatly within each individual predictor, depending on the other factors, e.g., mortality varied from 12% to 91% for completely immobile patients (CAS=0).


Own home
Nursing home
Age
BMI high/obese
BMI low/normal
BMI high/obese
BMI low/normal
Charlson Comorbidity Index
>3 3 2 1 0
>90 46 50 55 59 63 67 71 57 61 65 69 73 76 79 70 73 76 79 82 84 87 78 81 83 86 88 89 91
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65-70 8 10 12 14 16 18 21 13 15 17 20 22 26 29 20 23 26 30 33 37 41 28 32 35 39 44 48 52
65-70 7 9 10 12 14 16 18 11 13 15 17 20 23 26 17 20 23 26 30 34 38 25 28 32 36 40 44 48
65-70 5 6 7 8 9 11 12 7 9 10 12 14 16 18 12 14 16 19 21 24 28 17 20 23 26 30 34 37
6 5 4 3 2 1 0
Probabilities (%)
20 40 60 80
Cumulated Ambulation Score

Figure 6. (Opposite page) *Predicted 1-year mortality based on the final prediction model. Each small square represents a unique set of patient characteristics of the five variables included in the model. Colors indicate the risk and the small number in each square reports the predicted absolute mortality risk in percent. From Hjelholt TJ, Johnsen SP, Knudsen JS, Prieto-Alhambra D, Pedersen AB. Development and validation of a model for predicting mortality in patients with hip fracture. Age and Ageing. 2022;51. DOI: 10.1093/ageing/ afab233, Appendix II*[118].

Internal validation showed a moderate discrimination (AUROC = 0.74, 95% CI: 0.73 – 0.76). The calibration slope was 1.01 and the intercept -0.01, and visual inspection of the calibration plot was acceptable, although a slight overestimating of mortality risk in patients with the highest risk was noticed (Appendix II). In the sensitivity analysis, split sample validation based on geography and calendar year of operation showed similar results; the same did bootstrap validation, which also indicated that optimism correction of the AUROC would affect only the third decimal. This correction was therefore not performed. Finally, the MICE analysis showed results that were comparable to those of the main analysis.

5.3. Interaction effect of stroke history and hip fracture (Study III)

In this matched cohort study, we included 8,433 patients with a prefracture stroke history and hip fracture, 44,997 patients with hip fracture without a stroke history, 84,330 patients with a stroke history an no hip fracture, and 449,962 patients with neither stroke history nor hip fracture. Between 9.5% and 13.1% of the patients received pharmacological osteoporosis prophylaxis at the time of hip fracture/index date. Baseline characteristics of the four cohorts can be found in Appendix III. We found a positive interaction contrast of hip fracture and stroke on 0-30-day mortality of 18.2/100 PYs (95% CI: 7.5 – 28.8) (Figure 7, Appendix III).

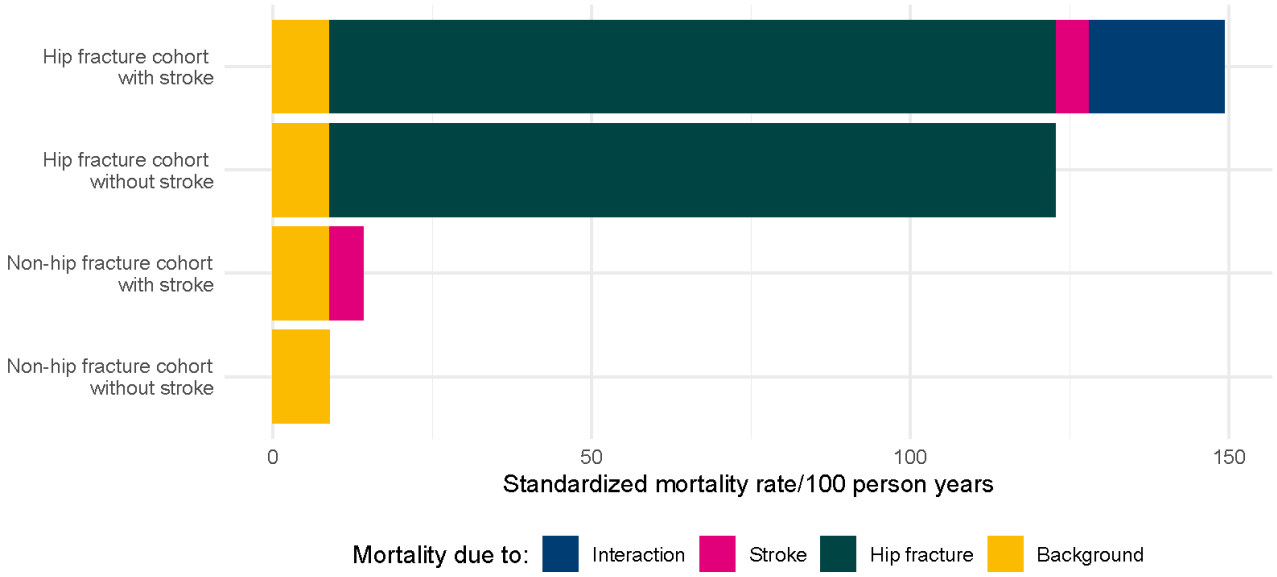

Figure 7. *Standardized mortality rate during the 0-30-day follow-up. From Hjelholt TJ, Johnsen SP, Brynningsen PK, Pedersen AB. The Interaction Effect Between Previous Stroke and Hip Fracture on Postoperative Mortality: A Nationwide Cohort Study. Clin Epidemiol. 2022;14:543-553. https://doi.org/10.2147/CLEP.S361507 (Appendix III)*[171].

At later follow-up times, we observed the same pattern but no interaction, viz. the lowest mortality in patients without hip fracture and without stroke, an increased mortality in patients without hip fracture and with stroke, a further increased mortality in patients with hip fracture without stroke, and the highest mortality in patients with hip fracture with stroke. On the multiplicative scale, we also detected a positive interaction for 0-30-day mortality, expressed by an attributable proportion of 9% (95% CI: 2.9–15.1) (Figure 8). No interaction was present at later follow-up times; however, the HR remained higher in patients with hip fracture with stroke than in the other groups.

Stratification on CCI level and patient age showed that interaction was most profound in patients with no other comorbidity (interaction contrast = 32.0/100 PYs (95% CI: 17.0–47.1), attributable proportion = 23.5% (95% CI: 13.9–33.1)) and in patients in the age categories 75-85 years (interaction contrast = 25.3/100 PYs (95% CI: 11.0–39.6), attributable proportion = 11% (95% CI: 0.0–22.0)) and 85-95 years (interaction contrast = 34.7/100 PYs (95% CI:13.2–56.2), attributable proportion = 10% (95% CI: 1.7–18.3)) (Figure 8, Appendix III). In the sensitivity analyses, more severe and more recent stroke were associated with higher interaction contrast and attributable proportion estimates, although the results were imprecise. Stratification on stroke type and inclusion of baseline medication as a confounding factor did not alter the results.

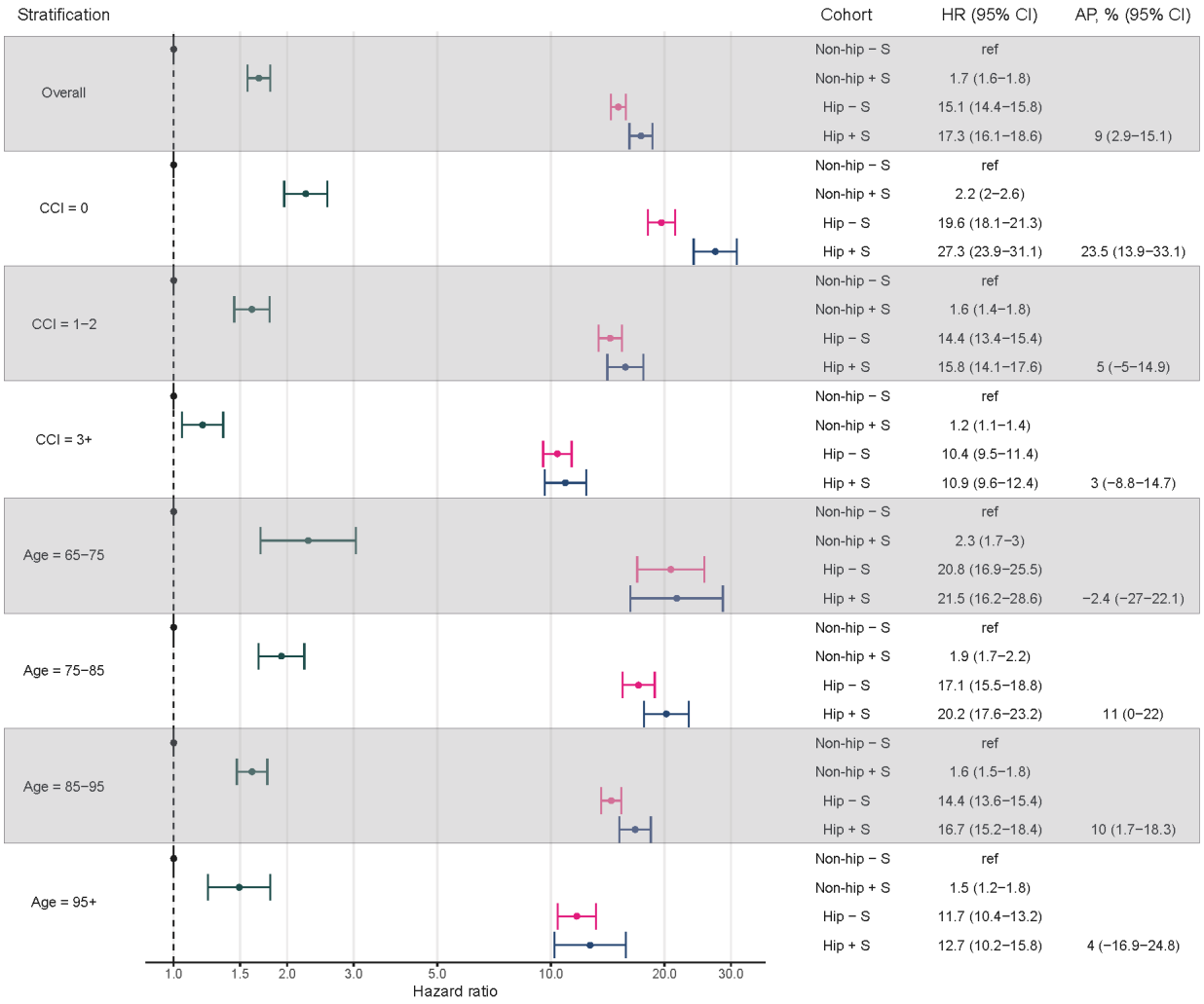

***Figure 8**. 0–30-day relative mortality, overall and stratified on comorbidity and age. Forest plot indicating the HR for 0–30-day mortality, whiskers indicating 95% CI. Patients without hip fracture and without stroke are used as a reference. From Hjelholt TJ, Johnsen SP, Brynningsen PK, Pedersen AB. The Interaction Effect Between Previous Stroke and Hip Fracture on Postoperative Mortality: A Nationwide Cohort Study. Clin Epidemiol. 2022;14:543-553. https://doi.org/10.2147/CLEP.S361507 (Appendix III)*[171].

5.4. Prefracture stroke history and the risk of recurrent fracture (Study IV)

The study population for Study IV, we included 48,230 individuals undergoing hip fracture surgery between 2011 and 2018. Among these, 4,128 (8.6%) patients had a prefracture stroke history within 5 years from hip fracture admission. Baseline characteristics of the population overall and divided by stroke history can be found in Appendix IV.

In the overall analysis, we observed a 1-year cumulative incidence of recurrent hip fracture in patients with a stroke history of 4.63 (95% CI: 3.94-5.39) vs 4.25 (95% CI: 4.05-4.47) in patients without a stroke history. After 2 years, the corresponding numbers were 6.29 (95% CI: 5.47-7.18) vs 6.12 (95% CI: 5.86-6.38) (Figure 9A).

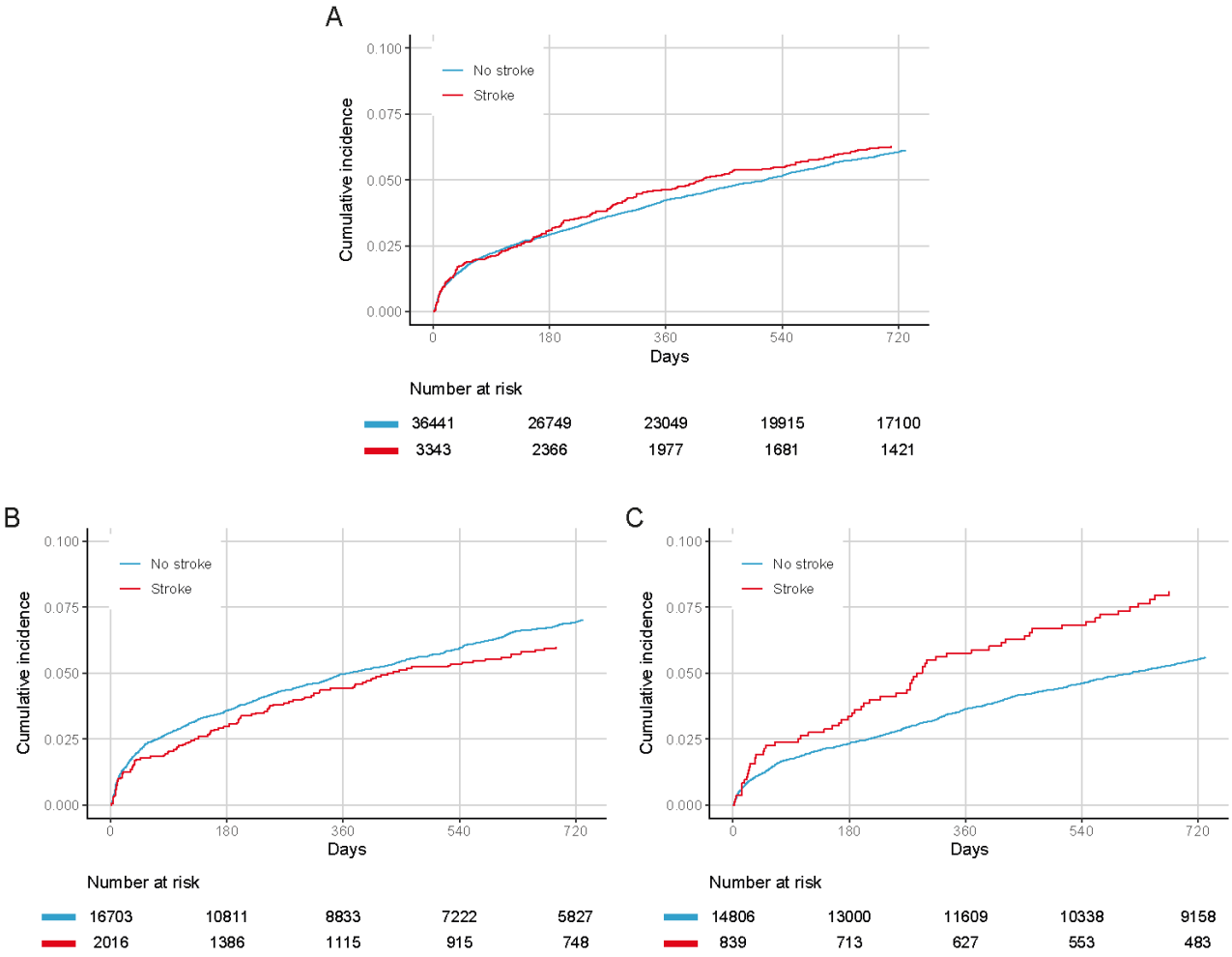

Figure 9. *Cumulative incidence of second hip fracture with death as competing risk among patients with/without a stroke history. Overall estimates (Panel A) and stratified on poor mobility (Panel B) and good mobility (Panel C). From Hjelholt TJ, Johnsen SP, Brynningsen PK, Andersen G, Pedersen AB. Impact of stroke history on the risk of recurrent hip fracture or major osteoporotic fractures among patients with incident hip fracture. A nationwide cohort study. Submitted to Journal of Bone and Mineral Research. (Appendix IV)*[172].

When the analysis was stratified on postfracture mobility, we observed that the 1-year cumulative incidence of second hip fracture among patients with good mobility and a stroke history was 5.76 (95% CI: 4.3-7.51) vs 3.66 (95% CI: 3.36-3.98) in patients without a stroke history. The corresponding 1-year cumulative incidences in patients with poor mobility were 4.42 (95% CI: 3.57-5.39) vs 4.99 (95% CI: 4.67-5.34). Expanding the follow-up time to 2 years did not change the results (Figure 9B-C).

Cause-specific adjusted HRs revealed the same picture. When we used patients without a stroke history as a reference, the HR in the overall analysis was 1.12 (95% CI: 0.94-1.32), whereas patients with a stroke history with good mobility had a HR of 1.55 (95% CI: 1.15-2.1) and patients with a stroke history with poor

mobility had a HR of 0.88 (95% CI: 0.7-1.1). We observed similar associations, although not as profound, for the outcome of major osteoporotic fractures (Appendix IV).

In the sensitivity analyses, more recent stroke and stratification on stroke severity did not alter the results. Adding the known covariates that could possibly introduce collider bias only changed the estimates from the Cox regression on the second decimal. Finally, the MICE analysis showed results that were comparable to those of the main analysis.

6

6. Discussion

Among older adults with hip fracture, we found a dose-response pattern with a variation in the 1-year risk of ischemic stroke from 1.5% to 8.6% depending on AF history and CHA_2DS_2-VASc score.[170] The predictive ability of the CHA_2DS_2-VASc score was moderate for ischemic stroke and poor for the other outcomes. In Study II, we successfully developed and validated a prediction model for 1-year mortality by combining five known risk factors that are easy to obtain at the time of admission: age, BMI, nursing home residency, CCI score, and CAS.[118] We also provided an intuitive and user-friendly risk stratification tool for clinical utilization. Finally, in Study III and IV, we presented solid evidence that a prefracture stroke history impacts the postoperative prognosis of patients with hip fracture, as shown in an excess short-term mortality,[171] an increased risk of recurrent hip fracture and major osteoporotic fractures among the 1- and 2-year survivors of hip fracture with a stroke history and good postoperative mobility.[172]

6.1. Risk of postoperative stroke (Study I)

6.1.1 Comparison with existing literature

Our results are in line with previously reported stroke incidences, averaging 4% – 5% in the first postoperative year following hip fracture.[11,88-91] The risk stratification offered by the CHA_2DS_2-VASc score combined with AF status can, however, provide a more qualified estimate with a 1-year risk varying from 1.5% to 8.6%.[170] Also corroborating previous results, the cumulative incidence curves presented in the present study indicate that the postoperative stroke risk is highest in the first days following operation, whereas they level off at day 10-15. Although speculative, this shift may be due to changes in the pathophysiological mechanisms; in the very early postoperative phase, perioperative risk factors such as hypotension and bone cement implantation syndrome may dominate, whereas, later on, after day 15, a more "classic" comorbidity-driven pathophysiology is present. The present study is, to our best knowledge, the first to estimate the risk of ischemic stroke based on AF and CHA_2DS_2-VASc in a population with hip fracture; consequently, the comparison is restricted to other studies with a similar methodology but conducted in other populations. In this context, patients with heart failure,[96] patients with ischemic heart disease,[98] and the general population[97,173,174] have been studied previously, and the results are comparable. Hence, a dose-response relationship exists with increasing CHA_2DS_2-VASc score, although it should also be acknowledged that the absolute risk difference between patients with AF and patients without AF varies according to study population. The modest discrimination for ischemic stroke found in this study[170] is close to the majority of previous reports in both populations with AF and populations without AF,[173,175] indicating that stroke prediction is a challenging task. The discrimination is, however, in line with the original validation of the CHA_2DS_2-VASc score[93] and with the external validation.[176]

6.1.2. Implications

This study provides evidence that the CHA_2DS_2-VASc score can be used for risk stratification for ischemic stroke in patients with hip fracture – irrespective of their AF status.[170] Patients with hip fracture represent a group of high-stroke-risk individuals. Remarkably, the lowest 1-year cumulative incidence was around 1.5%, which is above the normal threshold for considering administration of OAC to patients with AF.[94,95] Thus, our results suggest that more patients may benefit from OAC treatment – irrespective of their AF history. It should, however, be noted that our outcome does not distinguish embolic from thrombotic strokes, and OAC may be best suited for the first type. A previous study investigating the predictive value of the CHA_2DS_2-VASc score in non-AF community-dwelling adults found more than 20% of strokes to be of embolic pathophysiology.[174] Importantly, thromboembolic risk generally increases more than bleeding risk with rising age and increasing CHA_2DS_2-VASc score, which is reflected in an augmented net clinical benefit of treatment with Warfarin.[177,178] With the improved safety profile of DOACs, this ratio may benefit OAC even more.[179] Furthermore, a previous study showed reduced risk of both stroke and all-cause mortality in patients without AF with heart failure treated with OAC.[180] On the other hand, bleeding risk and patient preferences are also important factors to consider when evaluating the possible benefits of OAC.

In our study, among patients with AF who fulfilled the formal criteria for OAC treatment, only one of three patients was treated with OAC at baseline.[170] This is a concerning finding; and even though the introduction of DOACs has reduced this tendency,[181] underuse of OAC remains common and represents a missed opportunity to prevent morbidity and mortality due to ischemic stroke.

In conclusion, we demonstrated that the CHA_2DS_2-VASc score is a reasonable tool for evaluation of stroke risk among patients with hip fracture, regardless of their AF status. The stroke risk is generally high, which warrants careful consideration of pharmacological prophylaxis with either platelet inhibitors or OAC.

6.2. Prediction of postoperative mortality (Study II)

6.2.1 Comparison with existing literature

Compared with previously published prediction models for 1-year mortality,[103-107,182] the present study provides a substantially larger nationwide cohort from a 100% tax-funded hospital system. With the exception of the NHFS, previously published models are based on relatively small cohorts ($n < 1000$), which makes overfitting more likely, especially because the models have not been externally validated. The NHFS is by far the most tested model, even though validation data on 1-year mortality are only presented in three relatively small studies, with AUROCs varying between 0.66 and 0.78.[103,104,106] The NHFS has not achieved broad clinical implementation internationally, maybe because risk calculators are somewhat impractical unless they are well-known and well-integrated in clinical routine. Furthermore, the model only includes a few, selected comorbidities. Including a wider range of comorbidities or a comorbidity index such as the CCI

is, in our opinion, more relevant because comorbidity is very influential – and even more so when the follow-up time is extended to 1 year. A comorbidity index such as the CCI score can easily be calculated based on the available patient history in the electronic patient record and could even be automatically generated upon admission. Our model is the first to implement a broad comorbidity index combined with other important factors such as mobility and BMI.[118] Consequently, our model captures more aspects of the frailty syndrome, thereby making it more clinically relevant. Furthermore, the risk stratification tool presented in Figure 6 provides novel insight into the interplay between the different predictors included in the model, thereby extending the knowledge from previously published work. The sensitivity analysis presented in the present study[118] shows that the results are consistent across geographical and temporal trends in the cohort, while the bootstrap validation indicates that overfitting is marginal.

Contrasting most previous studies, sex was not an important and independent predictor in our study and it was therefore not included in the model.[118] Even though causal interpretation cannot be made directly from this setup, it could be speculated that male sex primarily serves as a proxy for other factors influencing a patient's prognosis, such as self-care, coping with illness, and treatment adherence; and that these factors are more strongly reflected in the other predictors.

The strong association between admission from nursing home and mortality has also been observed by others[102,105,182,183] and is most likely indicative of nursing home residents having more advanced disease and more severe disabilities.

The Hospital Frailty Risk score has, to the best of our knowledge, not previously been tested on Danish data. The score did not perform well in our cohort, and its discriminative power was lower than the discriminative power in the original validation.[145] This may be explained by the fact that the score consists of many different diagnoses including "factors influencing health status and contact with health services" (Z00-Z99). Coding of such factors are likely to be vary extensively across countries and regions and to reflect local practice, thereby limiting their usefulness in prediction models.

6.2.2. Implications

The yearly mortality of Danish individuals in percent, categorized by the age categories used in the model, is 1.4% at 65-70 years, 2.2% at 70-75 years, 3.8% at 75-80 years, 6.7% at 80-85 years, 11.5% at 85-90 years, and 22.9% at >90 years. Thus, the average mortality in the background population is within 4% – 5% of the lowest-risk category in the prediction model in each age category. However, as the other non-age predictors change to less advantageous combinations, the mortality increases substantially.[118] Whether this suggests a synergistic effect between the predictors and the hip fracture or if the hip fracture should be considered an event indicating severe clinical frailty has yet to be elucidated. Although a prediction model cannot prove causality, it may be speculated that a more aggressive optimization of comorbidity, nutrition, and

mobilization could reduce the excess mortality, thereby offering the patient a more beneficial 1-year prognosis. Potentially, the risk stratification tool in Figure 6 can be used to understand the interplay between the individual risk factors and how they act in concert to impact the prognosis.

We suggest that the visualization in Figure 6 may be used as a support tool to improve clinical decision making. When treating older adults with hip fracture, the challenging, but important, task exists of prioritizing medical treatments and re-evaluating pharmacotherapeutic indications. For such tasks, but also when evaluating the indication for new treatments, such as osteoporosis medication, or the relevance of cardiovascular drugs, clinicians are required to consider the patient's life expectancy. Even though the present model lacks external validation, we propose that it may serve as a tool that can aid clinicians when discussing these issues with the patient and their relatives. Physicians having experience with older and frail patients may intuitively perform such an evaluation of each individual; however, less experienced clinicians may benefit from this prediction model as a supportive tool, given the restrictions that always apply to the use of such models; they should never replace individual and sound clinical judgement.

In conclusion, we developed an intuitive risk chart for prediction of 1-year mortality in patients with hip fracture. This risk chart may be used as a supportive tool for clinical decision making. Furthermore, the study provides deeper insight into the interplay between the various predictors for mortality.

6.3. Interaction effect of stroke history and hip fracture (Study III)

6.3.1 Comparison with existing literature

In this large nationwide cohort study, we find prefracture stroke history to be a risk factor for postoperative mortality among patients with hip fracture, indicated by a higher MR and HR in the group of patients with both exposures compared with the other groups. This result is robust across short, intermediate, and long-term follow-up and also, with few exceptions among the oldest and most comorbid patients, across stratification on CCI and age categories.[171] This corroborates previous studies in the field, finding stroke to be a risk factor for mortality following hip fracture,[53,114,115] but it also contrasts others.[111,113,116] Of the three studies finding no association of stroke history, two were underpowered and provided rather imprecise estimates;[111,116] however, the point estimates of their regression analyses indicated a positive association. The third study presented data from 1987-2001,[113] and as the treatment of both stroke and hip fracture has improved considerably since then, comparison is difficult. Furthermore, the authors adjusted for mobility and limitations in functional level (activities of daily living). These factors are likely skewed between the exposure groups and may consequently (and mistakenly) be regarded as confounders. We find, however, that factors such as impaired mobility and reduced level of function are most likely a downstream consequence of the stroke and thus a mediator of the effect between stroke and mortality. If adjusted for, the part of the effect

mediated by these factors will be removed. In this case, we are investigating the total effect of stroke on mortality, and adjustment for these factors may explain the missing association.

6.3.2. Implications

This study provides strong evidence pointing towards prefracture stroke history as an independent risk factor for mortality at all follow-up times, thereby ending previous controversies on this issue. Furthermore, we extend current knowledge by presenting an interaction analysis showing an elevated interaction contrast and attributable proportion during 0-30 days of follow-up but not at later times.[171] This indicates an excess mortality, i.e., a mortality above what can be expected from hip fracture and stroke individually. Considering that the most important causes of short-term mortality in patients with hip fracture are acute postoperative complications, such as infections and cardiovascular events,[184] and that the risk of medical, cognitive, and psychiatric complications among stroke survivors is increased,[50,185,186] acute postoperative complications, such as delirium, infection, or cardiovascular events, may be important factors driving the excess mortality in patients with both conditions. This is important knowledge for clinicians as interventions can be designed to accommodate this increased risk, thereby possibly improving the prognosis for patients with hip fracture and a history of stroke.

Our results show that the interaction effect of stroke and hip fracture is pronounced in individuals with no or limited comorbidities (besides stroke).[171] With increasing comorbidity, the interaction effect is diminished, which indicates that the effect of stroke is diluted by other comorbidities. The age-stratified results showed no interaction between stroke history and mortality after hip fracture in the youngest and possibly fittest category of patients (age 65-75 years), whereas the interaction was high in the two middle-age categories (age 75-85 years and 85-95 years), and then disappeared among the oldest (age >95 years).[171] This should be interpreted with caution but may indicate that the oldest patients always have a very high mortality risk; and in this scenario, stroke plays a less dominant role.

Contrary to our hypothesis, the interaction effect disappeared in the later follow-up periods (31-365 days and 1-5 years). We anticipated to find a continued effect, based on an expectation of less profitable rehabilitation outcomes among patients with hip fracture and stroke history,[113,187] presumably impacting long-term survival; however, it may be speculated that the rapidly changing clinical status of older and frail patients with hip fracture makes such theoretically plausible associations difficult to observe.

Finally, the baseline finding that only around 10% of patients with a stroke history had received osteoporosis medication within the year before the index date is surprising and concerning. Underutilization of pharmacological osteoporosis prophylaxis in stroke survivors has received attention in published literature,[10,56,66,67] but, clearly, this issue warrants further exploration and clinical focus as the risk of hip fracture in patients with stroke history is high.[59,60]

In conclusion, this study provides strong evidence that prefracture stroke history is an independent risk factor for mortality in the first 5 years following hip fracture. Furthermore, we observed an interaction effect indicating excess mortality above what should be expected from the individual conditions only during 0-30 days of follow-up.

6.4. Prefracture stroke history and the risk of recurrent fracture (Study IV)

6.4.1 Comparison with existing literature

The overall 1-year cumulative incidence estimate of recurrent fracture of 4% – 5% found in the present study[172] is in line with estimates found in previous reports.[119,121-126,128,129] Importantly, our result corroborates the findings of a recent study that also used Danish data.[119] It does, however, somewhat contrast the 1-year and 5-year cumulative incidences of 9% and 20% found by Ryg et al.[120] This discrepancy is likely explained by two critical issues: Firstly, Ryg et al used the Kaplan-Meier method to estimate cumulative incidences and this method does not account for competing risks. Consequently, the Kaplan-Meier method is known to overestimate non-fatal outcomes in a setting with high mortality.[151,188] Secondly, recurrent fractures were defined differently by Ryg et al. Hence, they included all hip fracture diagnoses during follow-up that were matched with a relevant procedure code for hip fracture operation, whereas in the present study, we excluded fractures coded at the same site within six months, which is similar to the strategy pursued by Khalid et al in the two recent studies using Danish data.[119,128] Ryg et al report a 12-fold increased risk compared with the background population in the first month of follow-up. This estimate seems rather extreme and may indicate that our method is more efficient in excluding duplicate registrations, re-coding of the incident fracture, and reoperations.

To our knowledge this is the first study to explore the effect modification of baseline mobility on the association between stroke history and recurrent fracture. The explanation for this effect may lie in the logical consequence that if patients cannot be mobilized to standing position, the risk of falling will rely less on patient-related factors such as stroke history; and the risk will more likely depend on system-related factors such as safe patient lifting and moving and remembering to set up the guard rail when leaving the patient. In contrast, in patients with good mobility, the clinical characteristics of patients with stroke history, such as cognitive problems, may increase the risk of falling substantially due to uncritical behavior.

No previous study has investigated signs of collider bias in the context of risk of recurrent fracture. In our sensitivity analysis which addressed this issue, only a marginal change in estimates was found when the regression analysis was conducted adjusting for a wide range of possibly biasing factors. Although the risk of collider bias cannot be excluded on this basis, we find it reasonable to argue that the biasing effect is likely to be marginal, if present at all.

6.4.2. Implications

In the present study,[172] we corroborate previous findings suggesting that patients with hip fracture are a high-risk population in whom fracture-preventive interventions are relevant. Prophylaxis is especially important in patients with a stroke history and good mobility as the risk of recurrent fracture is even higher in this subpopulation. The risk of mortality and morbidity is increased following recurrent fracture compared with incident fracture[189] and, consequently, prevention of recurrent fractures is pivotal. In this context, the low prevalence of anti-osteoporosis treatment found in the present study is concerning; and this is even more alarming as treatment prevalence only improves marginally following incident hip fracture.[190] Anti-osteoporosis treatment must compete with numerous other important treatment indications as patients with hip fracture often have many comorbidities and a long medication list.[191] Consequently, well-indicated treatments are occasionally withheld because of side effects, interactions, or contraindications. Unfortunately, a uniform prevalence of anti-osteoporosis treatment in patients, regardless of comorbidity, level has been reported,[190] indicating that down-prioritization due to contraindication or interaction is not the only cause of the low treatment prevalence. Consequently, patients with incident hip fracture may benefit from an increased awareness of the benefits of anti-osteoporosis treatment, especially when considering the increasingly widespread utilization of intravenous Zoledronic acid administered once yearly.[192] This regimen has the potential to increase treatment initiation and adherence.[192] Other non-pharmacological interventions, such as hip protectors and environmental optimization, are also relevant considerations.

In conclusion, we found baseline mobility to be an effect modifier of the association between prefracture stroke history and recurrent fracture risk. This suggests different mechanisms for recurrent fracture depending on patient mobility and, consequently, the relevance of preventive interventions may vary between patients.

6.5. Methodological considerations

6.5.1. Study design

All studies in this dissertation are observational (non-experimental) cohort studies. A cohort is a group of individuals who share a common trait – in this case individuals older than 65 years who are undergoing hip fracture surgery in Denmark. A cohort study makes it possible to study large groups of individuals, which increases the precision in the estimates, and to study rare events or associations that would be unethical to investigate in an experimental design.[163] When utilizing the information-rich Danish health registries for such studies, large and cost-effective research projects can be conducted; however, important limitations must also be considered. First, the registries are not designed for research and, consequently, important information regarding the investigated associations may not have been recorded. This can potentially distort

the estimates. Second, other general limitations with the observational design must be considered. They will be discussed in the following sections.

6.5.2. Sources of bias in epidemiological studies

Bias can be divided into selection bias, information bias, and confounding.[163] All three types of bias can result in systematic error that challenges the internal validity of a study and results in flawed conclusions on the exposure-outcome relationship.[163] Random error, or chance, can also threaten the internal validity of a study and is usually evaluated via the statistical precision of the estimates, reflected in the 95% CIs.[163]

External validity reflects the generalizability of the results to a source population or patients with hip fracture in other countries.[163] For this to be meaningful, the internal validity is assumed to be high and the results of the study trustworthy. Generalizability can be affected by selection bias or by intentional selection of study participants with certain characteristics. All studies in this thesis used a nationwide cohort of patients, and we believe that our results are generalizable to patients with hip fracture in other industrialized western countries with comparable lifestyle and treatment regimens.[193] The population of Denmark mainly consists of individuals of European ancestry; however, we have no reason to believe that our results should be modified by ethnicity.

Selection bias

All four study populations were derived from national registries in a system with fundamentally free and equal access to health care.[135] Furthermore, follow-up is complete, as all residents in Denmark are accounted for via the Civil Registration System. Thus, we expect selection bias in these studies to be minimal. Certain considerations should, however, be mentioned. The completeness (sensitivity) of the DMHFR has never been investigated. The registry is expected to be almost 100% complete since reporting is mandatory for departments treating patients with hip fracture.[32] If correct procedure codes are not applied during admission, the patient would not be included. However, since departments are reimbursed for their activity through diagnosis and procedure codes, a certain focus on ensuring complete and correct coding is required, which speaks in favor of high completeness of the DMHFR. For any incompleteness to introduce bias, this would furthermore require that the non-included patients had a different association between exposure and outcome than the included patients, which seems unlikely.

Loss to follow-up is usually a major concern in cohort studies. If continued participation in the study is related to the exposure, a risk factor for the outcome, or the outcome itself, bias can occur.[163] We find this factor marginal in our studies due to the possibility to link the NPR to the Civil Registration System on the individual level. Consequently, almost all patients are accounted for during the entire follow-up period except a few individuals that emigrated (e.g., ≤5 individuals in Study I). In Study I and IV, which consider a

non-fatal outcome, the competing risk of death is an important factor that can lead to loss to follow-up. This factor is, however, handled via the relevant statistical methods as described in the methods section.

Missing data: In Study II and IV, the main analysis was based on complete cases only. Thus, cases reported to the DMHFR that did not include information on CAS, BMI, and type of residence at admission (Study II only) were excluded. This can be a source of bias if missing information is related to other factors.[194] The reason for missing data may theoretically be grouped into three categories; however, the terminology is not completely intuitive:[167,194] *Missing completely at random* denotes the situation where the reason for missing data is independent of both observed and unobserved factors, *missing at random* denotes the situation where the reason for missing data is related to observed variables, and *missing not at random* denotes the situation where the reason for missing data is related to unobserved variables. If data are missing completely at random, the complete case analysis is not biased, albeit the loss of power can be a problematic consequence.[167] In the two other instances, bias can arise - but only when data are missing at random can the missing values be imputed as described in section 4.7.8.[166,167] We find it reasonable to assume that data are partly missing completely at random, presumably because of busy departments with high patient loads resulting in occasional missing mobility tests or BMI measurements or simply forgetting or erroneous coding of the values. This can be more frequent at certain departments, but as all departments have a relatively large uptake area representing a broad variety of patient phenotypes, it will most likely cause data being missing completely at random. Furthermore, incomplete reporting may be more frequent when patients are more complex – i.e., a high comorbidity burden or a low performance status of the patient may result in more work for the health care professionals and consequently a higher risk that some variables are not reported. This will result in data being missing at random as we have rich information on other patient-related factors including comorbidity and medication use. No formal testing can prove that data are not missing not at random. However, based on the above explanations, we find it reasonable to believe that this factor plays only a marginal role.

Collider bias: This special form of selection bias can occur when (by design) we condition on patients having a hip fracture to be included in the study. Other factors that increase the risk of sustaining a hip fracture thereby become spuriously associated with the exposure (Figure 10). This bias would, however, only have the potential to influence our results

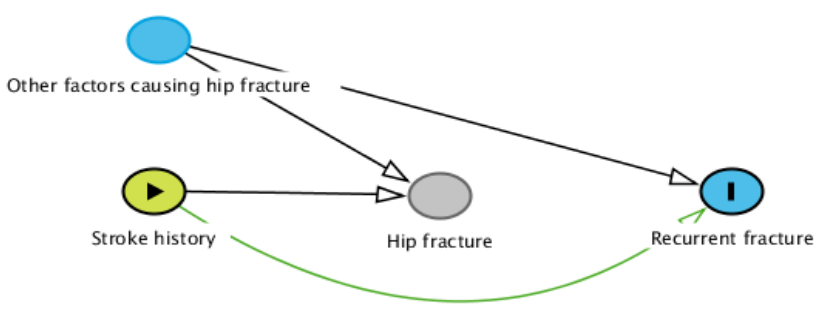

***Figure 10**. Directed acyclic graph illustrating collider bias in the context of Study IV.*

towards the null,[195] and, consequently, our estimates may be conservative. Furthermore, we adjusted the regression analysis for other known factors associated with falls and fractures in a sensitivity analysis in Study IV – this extra adjustment only changed the estimates on the second decimal. We find this to be an indication that collider bias is marginal.

Information bias

Misclassification of either exposure or outcome can lead to information bias. This type of bias can be non-differential (not related to other variables) or differential (i.e., misclassification of the outcome depends on the exposure). While non-differential misclassification can bias only towards the null (dichotomous outcome), differential misclassification can bias the association in both directions.[163] Correct classification of exposure, outcome, and covariates relies on several parameters, many of which cannot be directly investigated. Factors such as health-seeking behavior and surveillance bias can potentially affect the observed associations; however in most instances, the diagnoses of interest have been validated with a good result.

Misclassification of exposure: As a side project during this PhD, we validated the hip fracture diagnosis codes and surgical procedure codes in the DMHFR (and the NPR).[196] Overall, we found all patients to have sustained a hip fracture, meaning that the overall positive predictive value (PPV) was 100%. For the specific fracture and operation types, the PPVs were generally above 90%.

The exposures used in the four studies in this thesis have been validated in the NPR. This includes stroke diagnoses,[197,198] showing PPVs of 79% – 93% for stroke overall and 88% for the ischemic stroke subtype. Of some concern, our data indicate a decreasing stroke incidence with increasing age (Figure 11). This sharply contrasts with the general consensus pointing at increasing age as an important risk factor for stroke.[199] This could indicate that surveillance bias influences the registration of strokes, i.e., that fewer strokes are recognized and registered as patients become older - perhaps due to increased comorbidity and disability with age, resulting in a less clear symptomatology. A competing risk of death could also explain the observed pattern in Figure 11A; however, when inspecting the cumulative incidence curves in Figure 11B, this does not seem to be the case. In Study I, a misclassification of stroke exposure related to age and comorbidity would most likely introduce a bias towards the null (we would observe a lower CHA_2DS_2-VASc score and, thus, a less clear dose-response association with the outcome). In Study III and IV, this misclassification would also bias the results towards the null.

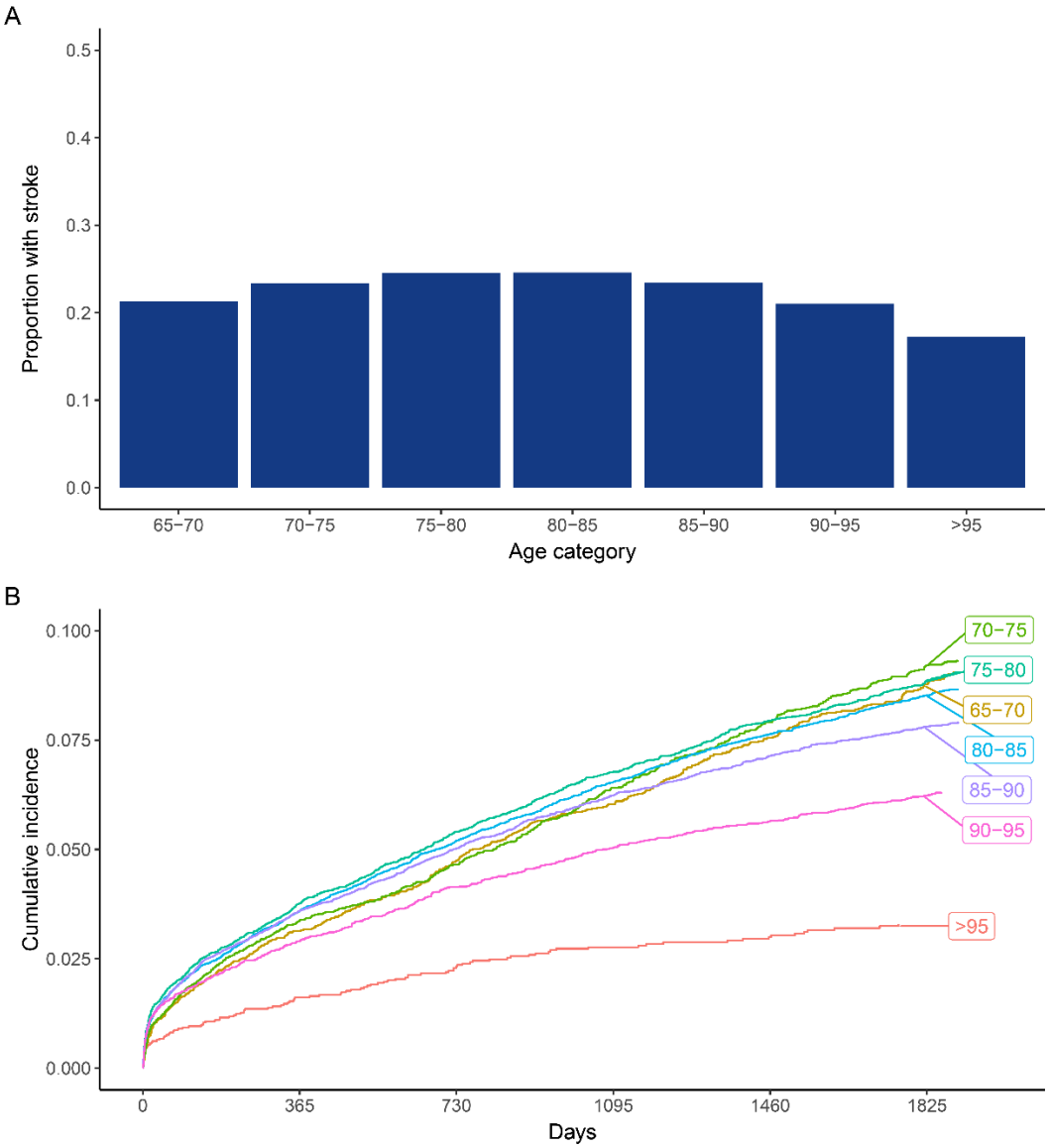

Figure 11: *Panel A: Proportion of patients with stroke (both pre- and postfracture) according to age category at the time of admission with incident hip fracture. Panel B: Cumulative incidence of ischemic stroke outcome with death as competing risk during 5 years of follow-up according to age category.*

The 19 disease categories of the CCI have also been evaluated,[200] showing an overall PPV of 98% with variation from 82% to 100%. The completeness of the CCI is, however, unknown. Considering that some of the diseases included in the index have been increasingly handled by the general practitioner in recent decades, the completeness might be moderate in some instances. It could be speculated that the simple patients may to a greater extent be handled by the general practitioner. If this was the case, this would cause differential misclassification. As the CCI score was used as a predictor for mortality in Study II and for covariate adjustment in Study III and IV, the differential misclassification could affect the estimates of the

regression analyses in both directions. Despite this drawback, we have shown acceptable discrimination of the CCI combined with age and gender for prediction of 30-day and 1-year mortality in patients with hip fracture.[201] The coding algorithm used in the CCI was also used for the relevant diseases in the CHA_2DS_2-VASc score (C, D, S_2, and V), whereas age and sex were derived from the CPR number and consequently assumed to be 100% correct. Hypertension has been validated in the NPR;[202] however, the validity of the combination of dispensed antihypertensives and diagnoses from the NPR is not known.

Misclassification of outcome: In Study I, the main outcome was ischemic stroke, which is discussed above. Misclassification of ischemic stroke related to increasing age would bias the results towards a less clear dose-response association between the CHA_2DS_2-VASc score and ischemic stroke.

In Study II and III, the outcome was mortality. Information on mortality was obtained from the Civil Registration System, which is considered a highly valid administrative database. Consequently, we expect the risk of misclassification in this regard to be very limited.

Recurrent fracture was the main outcome in Study IV; and although we have validated the hip fracture diagnoses in the NPR, the validation only encompassed incident fractures. When dealing with recurrent fractures, the risk of misinterpreting a re-coding of the incident fracture as a recurrent fracture is present. This risk would most likely increase every time the patient is readmitted to hospital because new registrations are made at every admission. As patients with more comorbidities are admitted to hospital more often than patients without comorbidity, this could cause differential misclassification of the outcome related to, e.g., the CCI score. To avoid this misclassification, we excluded all registrations of fractures coded at the same site in the first 6 months of follow-up; however, this method has never been validated.

Confounding

To fulfill the confounder criteria, factors should be associated with both the exposure and the outcome but cannot be an intermediate step on the exposure-outcome pathway.[163] Known confounders are usually identified using DAGs and handled either by design (e.g., randomization or matching) or in the analysis (e.g., standardization, stratification, or adjustment of regression analyses). Even though the known confounders were dealt with using these methods, residual confounding due to misclassification of information on the confounder can still affect the observed association. For instance, misclassification of the CCI score in Study III could result in residual confounding, even though the Cox analysis was adjusted for this factor. Also, in Study III, we performed the analyses stratified on CCI categories, but the Cox analysis was also adjusted for CCI score (continuous variable) to further minimize residual confounding that may reside within each category. A complete overview of the potential confounders in each study and how they were handled can be found in Table 2.

Unmeasured confounding denotes confounding caused by unobserved variables. A drawback of epidemiological studies using the Danish health registries is missing information on lifestyle factors such as smoking, alcohol consumption, and physical activity. These factors are related to the risk of osteoporosis, fractures, and stroke. Occasionally, a proxy can be used to indicate the extent to which such a factor would influence the result. For instance, in the sensitivity analysis performed in Study I, we used a diagnosis of chronic obstructive pulmonary disease to reflect smoking – which showed no impact on the results when adjusting for this extra variable.

In Study II, we developed a prediction model. Patient-related factors that can confound the association were therefore not an issue. Factors threatening the validity of the results might have remained, but they were handled in the validation process. To ensure the robustness of our results across calendar time and geographical variation, we performed sensitivity analysis where data were split on these factors for development and validation of the model.

6.5.3. Statistical considerations

All statistical methods used in this thesis are well described in international literature; however, a few subjects require further discussion.

Variable selection (Study II)

When choosing which predictors to include in a prediction model, several methods can be applied.[108] First, subject knowledge can reduce the number of candidate predictors considerably; and, in our case, a decision on when and how we considered the model relevant to use also guided the choice. The most commonly used and well-described methods include forward - and backwards selection and "least absolute shrinkage and selection operator", or LASSO, regression.[108] We chose to use a method that has not received as much attention, although it provides a very transparent and intuitive selection process. The variable importance plot provides a method to easily understand and visualize which predictors are most influential.[158] The interpretation of the plot depends on the applied model; however, when comparing the individual predictors, this detail is less important if the model and, in our case, the splitting criterion in the decision tree are relevant.[157] The 25% cut-off value of relative importance was arbitrarily chosen. Still, to ensure that predictive performance was not lost, we applied a backward selection process for the variables below the cut-off with AUROC as the selection criterium.[108] To our knowledge, this combination of methodologies for variable selection has not been attempted in prior studies. The individual methods are within a standard statistical approach and as it provided the reader and us with knowledge on how the individual predictors performed and affected each other, we found it to be a good approach.

Traditional Cox regression vs. competing risk regression (Study I and IV)

When analyzing time-to-event data with competing risk, the two most well-described regression methods are the Cox regression model and the competing risk regression model, also known as the Fine and Gray model.[151] Both models provide a HR estimate; however, the interpretation is somewhat different depending on the model. In both Study I and Study IV, we used the traditional Cox regression, meaning that the individuals who sustain the competing event (death) were censored at that time and therefore did not contribute to the denominator of later risk sets.[151] Thus, the estimates, commonly referred to as the cause-specific HR, reflect only individuals who are alive and at risk of the outcome at the given time, but the estimates do not account for the HR of the competing event at the same time; consequently, the relation between the cause-specific HR and the relative risk depends on the hazard of sustaining the competing event.[151,153] The Cox approach does, however, address the population of primary clinical interest.[203] If estimates should be used for prediction, the Fine and Gray approach would be more suited.[153] The estimates from this model directly reflect the relative relationship between exposure groups of the cumulative incidence function where individuals who sustain the competing event are kept in the denominator in future risk sets. Thus, the estimate from the Fine and Gray model, commonly referred to as the subdistribution HR, takes into account the risk of the competing event. It has, however, shown to produce some rather contra intuitive estimates in settings with a high risk of the competing event.[203]

Statistical power

Even though all studies in this thesis included more than 20,000 individuals, the statistical precision of the estimates became low when the outcome was rare and when the analyses were stratified on other variables. This resulted in relatively wide 95% CIs in some instances. To obtain as much power and precision as possible, we included the largest population obtainable. However, we were restricted to use only the time periods recording relevant variables for our association. In Study IV, we used a study period from 2011-2018 because the CAS score was not included in the dataset before 2011. It would have been preferable to use the entire period of the DMHFR, which we did in Study I, as this would have doubled the size of the study population. Furthermore, the missing values in Study IV resulted in a further reduction in size of the study population in the regression analysis. To counter this, we did a sensitivity analysis with imputed values, thereby increasing the study population from 34,364 to 48,230. However, because the MICE analysis included some element of imprecision in the imputed estimates, the final estimates of the investigated association were not more precise. Power calculations were not performed in the planning of any of the studies.

7. Overall conclusions

Based on the four studies presented in this thesis, we conclude that:

1) The postoperative risk of ischemic stroke and thromboembolism is very high in patients undergoing hip fracture surgery. The CHA_2DS_2-VASc score provides a useful tool to predict the 1-year risk of ischemic stroke among patients with hip fracture, irrespective of AF history. Based on the absolute risks found in this study, it may be appropriate to reconsider the relevance of OAC for a larger part of this population.

2) The CHA_2DS_2-VASc score, however, was a poor predictor of 1-year mortality. We therefore developed and validated an intuitive risk chart for prediction of the 1-year mortality among patients with hip fracture using only five predictors: Age, BMI, nursing home residency, CCI score, and CAS. This risk chart provides novel information on the interplay between the five predictors. In addition, the it can serve as a supportive tool for clinical decision making.

3) Prefracture stroke history is an important risk factor for postoperative mortality and recurrent hip fracture in patients with incident hip fracture. Interaction between stroke history and hip fracture resulting in excess mortality above what could be expected from the individual diseases was present only in the first 30 days of follow-up. Risk of recurrent fracture was modified by patient mobility, suggesting that different mechanisms of action exist in patients with good versus impaired mobility.

8. Future perspectives

To further uncover the pathophysiological mechanisms driving the increased ischemic stroke risk in the early postoperative phase following hip fracture, it is essential to conduct studies focusing on perioperative risk factors with detailed clinical data on timing and duration of fluctuations in arterial blood pressure, ultrasound data on emboli formation, and cardiac performance parameters. Such data may provide important information on the prevalence of these theoretically plausible perioperative complications and their clinical consequences. Furthermore, if feasible, it could be very interesting to conduct an interventional study investigating the beneficial effect of OAC, regardless of AF status.

The risks and potential areas for intervention among patients with a prefracture stroke history are other important issues that merit further investigation. In this regard, it would be valuable to study the short-term complications following hip fracture, comparing patients with and without a stroke history. Further understanding of the risk of recurrent fracture may be obtained by a cognitive evaluation of patients during hip fracture admission. Poor cognition and postoperative delirium often play a critical role in these patients. Unfortunately, such data are not routinely recorded. Moreover, having shown the effect of basic mobility on the association between stroke history and recurrent fracture, we argue that more detailed measures of mobility could potentially elucidate which specific domains (e.g., balance or muscle power) play the most crucial role, thereby directing future interventions.

Knowing that pharmacological prophylaxis of osteoporosis has the potential to reduce the risk of hip fracture substantially, it may be beneficial to conduct a study investigating the use of intravenous Zoledronic acid, which is administered only once per year, as a potentially safe and effective treatment during the index admission.

The prediction model from Study II requires external validation to further document its robustness. Geriatric colleagues suggested to test the model as a learning tool against the experienced consultants' clinical judgement of patient prognosis. Testing model performance on both shorter and longer follow-up duration would also be a natural extension of the current application; however, this may require a repeated evaluation of relevant predictors considering that the mechanisms and influencing factors on mortality may have a different weight if the timeframe is changed.

9

9. Summary

Proximal femur fracture, commonly known as hip fracture, and acute stroke are common conditions among older persons. Both conditions have an unfavorable prognosis due to high mortality, reduced mobility, and increased dependence. Even though strong evidence of an increased fracture risk following stroke exists, it remains disputable whether older persons with a history of stroke have a worse prognosis following hip fracture than older persons without such a history. Some papers also report an increased cardiovascular risk in the early postoperative phase following hip fracture surgery, but the factors driving this increased risk are sparsely investigated.

In this thesis, we investigated risk factors for postfracture stroke (Study I) and developed a prediction model for postfracture mortality (Study II). We also examined the impact of a prefracture stroke history on the prognosis following hip fracture (Study III and IV). All studies are population-based cohort studies based on the Danish Multidisciplinary Hip Fracture Registry.

In study I, we evaluated the association between the CHA_2DS_2-VASc score (congestive heart failure, hypertension, age ≥75 years (2 points), diabetes, previous stroke/transient ischemic attack/systemic embolism (2 points), vascular disease, age 65-74 years, and female sex) and the risk of ischemic stroke, thromboembolism, and death. We found a 1-year cumulative incidence of stroke of between 1.5% and 8.6% depending on the CHA_2DS_2-VASc score. At scores above 3, we found a dose-response association.

In Study II, we developed and validated a prediction model for 1-year mortality. Using a decision tree model to establish the importance of each independent predictor, we selected the five most influential factors for the final model. We presented the model in an intuitive risk chart that can easily be implemented in daily clinical work. The model predicts the mortality risk, spanning from 5% to 91%, and it visualizes the interplay between the different predictors.

Finally, we compared patients with hip fracture with and without a prefracture stroke history in terms of their risk of mortality (Study III) and recurrent fracture (Study IV). We found that stroke history was a risk factor for postoperative mortality after 30 days, 1-, and 5 years. We also observed a mortality in excess of what could be expected from the individual diseases (interaction) after 30 days only. Stroke history was a risk factor for recurrent fracture primarily among patients with good mobility following the incident hip fracture.

In conclusion, we found a high risk of postoperative stroke in patients with hip fracture, and the CHA_2DS_2-VASc score was a useful tool with which to evaluate ischemic stroke risk. We developed a novel prediction model to estimate 1-year mortality risk in patients with hip fracture, visualized as an intuitive risk chart. Finally, we establish that prefracture stroke history is an independent risk factor for mortality, whereas the risk of recurrent fracture is modified by patient mobility.

10. Dansk resume (Danish summary)

Hoftefraktur og apopleksi er hyppige tilstande blandt ældre mennesker. Begge tilstande har en dårlig prognose med høj mortalitet, reduceret funktionsniveau og øget afhængighed af hjælp. Til trods for at der foreligger solid evidens for en øget risiko for hoftefraktur blandt patienter med apopleksi, er der usikkerhed om, hvorvidt prognosen er dårligere for de patienter med hoftefraktur, som tidligere har haft en apopleksi, end blandt de patienter med hoftefraktur, som ikke tidligere har haft en apopleksi. Derudover har enkelte studier peget på en øget apopleksirisko i den tidlige postoperative fase efter operation for hoftefraktur, men risikofaktorerne herfor er dårligt belyste.

I denne afhandling har vi undersøgt risikofaktorer for potoperativ apopleksi (Studie I) og udviklet en prædiktionsmodel for 1-årsmortalitet efter hoftefraktur (Studie II). Derudover har vi udforsket, hvordan præfraktur apopleksihistorik påvirker prognosen efter hoftefraktur (Studie III og IV). Alle studier er populationsbaserede cohortestudier baseret på det danske tværfaglige register for hoftenære lårbensbrud.

I Studie I vurderede vi associationen mellem scoren for CHA_2DS_2-VASc (congestive heart failure, hypertension, age ≥75 years (2 points), diabetes, previous stroke/transient ischemic attack/systemic embolism (2 points), vascular disease, age 65-74 years, and female sex) og risikoen for iskæmisk apopleksi, tromboemboli og død. Den kumulerede incidens for apopleksi inden for det første år varierede mellem 1,5% og 8,6% afhængigt af CHA_2DS_2-VASc-scoren, og for scorer over 3 sås en dosis-responssammenhæng.

I Studie II udviklede og validerede vi en prædiktionsmodel for 1-årsmortalitet. Ved at bruge en *decision tree model* kunne vi estimere den relative vigtighed af hver uafhængig prædiktor, og vi udvalgte de 5 vigtigste til den endelige prædiktionsmodel. Vi præsenterede modellen som et intuitivt risikostratificeringsskema, som let vil kunne implementeres i klinisk praksis. Modellen prædikterer en mortalitetsrisiko mellem 5% og 91%, og skemaet visualiserer desuden sammenspillet mellem de individuelle prædiktorer.

Endelig sammenlignede vi risikoen for mortalitet (Studie III) og ny hoftefraktur (Studie IV) i patienter med hoftefraktur med og uden præfraktur apopleksi. Vi fandt, at apopleksi var en risikofaktor for postoperativ mortalitet efter opfølgning i 30 dage, 1 år og 5 år. Derudover fandt vi efter 30-dagesopfølgningen en overdødelighed ud over hvad, der kan forventes ud fra hver enkelt tilstand (interaktion). Apopleksihistorik var primært en risikofaktor for ny hoftefraktur blandt patienter med god mobilitet efter første fraktur.

Vi konkluderer, at der er en høj risiko for postoperativ apopleksi blandt patienter med hoftefraktur, og at CHA_2DS_2-VASc-scoren kan anvendes til at vurdere denne risiko. Vi har udviklet en ny prædiktionsmodel for 1-årsmortalitet, og har visualiseret denne i et intuitivt værktøj til risikostratificering. Derudover finder vi, at præfraktur apopleksihistorik er en selvstændig risikofaktor for mortalitet, hvorimod risikoen for ny hoftefraktur er modificeret af patientens mobilitet.

11. Supplementary tables

Table S1. Papers relevant for Study I. Listed papers report on incidence of postoperative stroke (main outcome) among patients with hip fracture and/or risk factors associated with an increased risk of this outcome

Study I: Risk of postoperative stroke following hip fracture surgery			
Author, Journal, Year	**Design, setting, period**	**Study population, exposure, outcome**	**Results, comments**
He, et al[204] **BMC geriatr** **2022**	Cohort study Chengdu, China 2017-2020	n = 2,517 having total hip arthroplasty after hip fracture Exposure: Patient demographics, comorbidity, biochemistry Outcome: Ischemic stroke within 90 days Statistics: Logistic regression	2.5% with ischemic stroke Risk factors: Age, Diabetes, Hyperlipidemia, AF, D-dimer Comments: Only patients with arthroplasty. No information on cemented vs uncemented, only 70 years or older. No information on medication
Dubin, et al[205] **Medicine (Baltimore)** **2022**	Cohort study Level 3 trauma center, Israel 2003-2014	n = 250 Exposure: Surgical procedure. Bipolar hemiarthroplasty vs. cannulated screw Outcome: Cerebrovascular accident within 2 years Statistics: Chi-squared test within each exposure group to test for difference in outcome	Indication of fewer cerebrovascular accidents in the hemiarthroplasty group Comments: No comparison between exposure groups, No mention of timing of the outcome, and no considerations of a pathophysiological mechanism for the association between surgical procedure and late postoperative cerebrovascular accidents. No inclusion of possible confounders in the analysis

Wang, et al[206] **J Healthc Eng** **2021**	Cohort study Shandong, China 2017-2021	n = 240 Exposure: General anesthesia Outcome: Ischemic stroke, perioperative heart rate and mean arterial pressure Statistics: t-test between groups, logistic regression	Postoperative stroke occurred in 28.3% of the general anesthesia group vs. 5.0% in the non-general anesthesia group General anesthesia group had higher heart rate and lower mean arterial pressure Comments: Very selective in- and exclusion criteria, not clear whether this is an interventional or observational study, follow-up time not stated, type and dose of anesthetic drugs not stated. Confounding by indication not considered
Wahlsteen, et al[207] **Age and Ageing** **2021**	Cohort study Nationwide Danish health registries 2000 - 2017	n = 124,660 Exposure: Comorbidities and medication use Outcome: Stroke and myocardial infarction Statistics: Cumulative incidences (death as competing risk), Cox regression	Previous stroke and AF were independent risk factors for postoperative stroke Heart failure, hypertension, diabetes, and chronic kidney disease were identified as risk factors in women only Comments: No explanation for divergent findings between men and women
Ogawa, et al[71] **Clin Interv Aging** **2021**	Propensity score matched cohort study Japanese Diagnosis Procedure Combination inpatient database 2010 - 2016	n = 15,666 receiving cemented hemiarthroplasty matched 1:1 with patients receiving cementless hemiarthroplasty. All patients had femoral neck fractures Outcome: All-cause mortality, cardiovascular complications	Increased 1-10-day mortality in the cemented vs uncemented group Increased risk of in-hospital stroke and ICU admission in the cemented group Comments: No information on VTE prophylaxis, no association of cementation on pulmonary embolism

		Statistics: Propensity score matching (logistic regression), Cox regression	
Yu, et al[92] **J Orthop Surg Res.** **2020**	Cohort study Single center study; patients surgically treated for a hip fracture in 3rd Hospital of Hebei Medical University, China 2014 - 2018	n = 3,743 Exposure: Patient demographics, comorbidity, comedication, biochemical markers Outcome: stroke identified during hospital stay or via telephone interview at 1-, 3-, 6- and 12-months postsurgery Statistics: Logistic regression	56 patients (1.5%) had a stroke during follow-up. Independent risk factors: Increasing age, stroke history, ASA III or higher, long-term aspirin use and elevated red blood cell distribution width Comments: No data on patients excluded due to incomplete follow-up or death from other causes. Competing risk of death not considered
Bohsali, et al[208] **J Am Acad Orthop Surg** **2020**	Cohort study US Nationwide Inpatient Sample (NIS) 2005-2013	n = 2,020,712 Exposure: History of heart failure (preserved ejection fraction (n = 31,118), reduced ejection fraction (n = 22,267)) Outcome: Major adverse cardiovascular and cerebrovascular event Statistics: Logistic regression	Both types of heart failure increased risk of peri- or post operative stroke Comments: Follow-up time not stated, death as competing risk not considered, no absolute estimates
Samuel, et al[209] **Orthopedics** **2018**	Cohort study National Trauma Data Bank 2011-2012	n = 37,584 Exposure: Patient demographics, comorbidity, systolic blood pressure, fracture type, procedure type Outcome: In-hospital stroke Statistics: Proportions of the outcome, logistic regression	In-hospital stroke: 0.4% Risk factors: Stroke history, known coronary artery disease, bleeding disorders, and systolic blood pressure >180 mmHg Comments: Follow-up time not stated, death as competing risk not considered

Atzmon, et al[88] **J Orthop Surg Res.** **2018**	Medical record review Meir Hospital Sapir Medical Center, Israel 2003 - 2014	n = 2,195 Exposure: Patient demographics, comorbidities, OAC use, surgical delay, LOS, rehabilitation protocol Outcome: 5-year postoperative stroke Statistics: Kaplan-Meier analysis, logistic regression	110 patients (5%) had postfracture stroke, 83 (3.8%) with no prefracture stroke Risk factors: Arterial hypertension, AF, diabetes Patients with stroke had increased mortality Comments: Unadjusted analysis only, death as competing risk not considered
Pedersen, et al[11] **J Bone Miner Res.** **2017**	Cohort study Nationwide Danish health registries 1995 - 2015	n = 110,563 (552,774 general population controls) Exposure: Age, gender, and comorbidities Outcomes: Stroke and myocardial infarction (0-30 days and 30-365 days) Statistics: Cumulative incidence (death as competing risk), Cox regression, interaction contrast	0-30 days and 1-year stroke incidence: 2.2% and 4.3% Elevated stroke risk compared with controls. 0-30 days and 1-year aHR 9.42 and 2.27 Interaction between comorbidity and stroke risk (Attributable proportion) up to 17.6% (0-30 day) Comments: No distinction between stroke specific and non-specific risk factors
Tsai, et al[91] **Osteoporos Int.** **2015**	Cohort study Taiwan National Health Insurance Research Database (LHID2000) 2000 – 2011	n = 6,013 (23,802 non-hip fracture controls), stroke history = exclusion criterion Exposure: Patient demographics, comorbidities, comedications Outcome: Stroke, divided into ischemic and hemorrhagic (follow-up time: 1, 2-3, 4-5, >5 years) Statistics: Kaplan-Meier method, Cox regression	1-year stroke incidence: Approx. 5% (read from graph), aHR 1.96 compared with controls Risk factors: Any comorbidity, cardiovascular comorbidities, medication use Comments: 23% of patients below 65 years. (Mean age 72 years), no distinction of AF, death as competing risk not considered
Kang, et al[90] **Stroke** **2011**	Cohort study Taiwan National Health Insurance Research Database (LHID2000)	n = 2,101 (n = 6,303 non-hip fracture controls), stroke history = exclusion criterion Exposure: Patient demographics, comorbidities Outcome: 1-year stroke	1-year stroke incidence: 4.1%, aHR 1.53 compared with control group Risk factors: Cardiovascular comorbidities

	2001 – 2005	Statistics: Kaplan-Meier method, Cox regression	Comments: More than 32% of patients below 65 years (Mean age 77 years), no distinction of AF, death as competing risk not considered
Popa, et al[89] J Hosp Med. 2009	Cohort study Tertiary Center in Olmsted County, Minnesota 1988 – 2002	n = 1,606 (1.195 fracture repairs and 691 THA) Exposure: Fracture vs THA, Patient demographics, comorbidities, comedication Outcome: 1-year stroke risk Statistics: Kaplan-Meier method, Cox regression	1-year stroke incidence 5.5% Elevated stroke risk among hip fracture vs THA patients (HR 3.80) Risk factors: Previous stroke, AF, aspirin use Comments: Imprecise estimates, death as competing risk not considered
Lawrence, et al[21] Arch Intern Med 2002	Cohort study 20 US hospitals (academic, community and Veterans Affairs) 1982 – 1993	n = 8,930 Exposure: In-hospital medical complications (until discharge, death, or 30 days postoperative) Outcome: 30-day and 1-year mortality Statistics: Proportions of medical complications	85 patients (1%) had TIA or stroke during the in-hospital follow-up 4-10-fold higher mortality among stroke patients vs. overall Comments: Mainly descriptive study, no associations or regression models, poorly defined follow-up period

Abbreviations: AF: Atrial fibrillation, (a)HR: (Adjusted) hazard ratio, LOS: Length of stay, OAC: Oral anticoagulant therapy, VTE: Venous thromboembolism

Table S2. Papers relevant for Study II. Listed papers report on risk factors for 1-year mortality among patients with hip fracture

Study II: Prediction of postoperative mortality – known risk factors			
Author, Journal, Year	**Design, setting, period**	**Study population, exposure, outcome**	**Results, comments**
Xing, et al[210] **Front Med** **2022**	**Cohort study** **West China Hospital, China** **2013-2017**	n = 591 Candidate risk factors: Patient demographics, BMI, comorbidities, fracture type, operation type, perioperative blood loss/transfusion, biochemistry Outcome: 1-year mortality Statistics: Random forest model, logistic regression model. Split sample validation for AUROC	Overall 1-year mortality: 14.7% Risk factors included: Age, time to surgery, COPD, albumin, hemoglobin, history of malignancy, perioperative blood transfusion AUROC from for random forest: 0.81, logistic regression: 0.78 Comments: Very low mortality – selection? No calibration data shown. Suspect overfitting (relatively small, single-center study)
Kitcharanant, et al[211] **BMC Geriatr**	Cohort Study Siriraj Hospital, Bangkok, Thailand 2016-2018	n = 492 Candidate risk factors: Patient demographics, BMI, CCI, fracture type, operation type, mobility, use of walking aid Outcome: 1-year mortality Statistics: Seven different machine learning algorithms were tested. Split sample validation for AUROC and calibration	Overall 1-year mortality: 12.6% All risk factors included in the models AUROC from 0.81 (K-nearest neighbor) - 0.99 (Random forest) Comments: Very low mortality – selection? No calibration data shown. Suspect overfitting (relatively small, single-center study)
Frandsen, et al[183] **Eur Geriatr Med**	Cohort Study	n = 2,800	Overall 30-day mortality: 9%, 1-year: 24%

2022	Holstebro Hip Fracture Database 2011-2017	Candidate risk factors: Patient demographics, ASA grade, biochemistry, BMI, fracture type, operation type, mobility, dementia Outcome: 30-days and 1-year mortality Statistics: Logistic regression	Risk factors found: Age, male sex, nursing home residence, BMI, albumin, creatinine, dementia, poor mobility, no mobilization 24 h postoperative Comments: No prediction modeling, no combined absolute estimates
Van de Ree, et al[105] **Hip Int** **2020**	Cohort study Two Dutch hospitals + Dutch Trauma Registry Jan 2009 – Dec 2013	n = 925 Candidate risk factors: Patient demographics, Hgb, mobility, fracture type, ASA grade, comorbidities, cognitive frailty Outcome: 30-day and 1-year mortality Statistics: Logistic regression, AUROC, H&L test	Overall 1-year mortality: 25% Risk factors included: Age, sex, living in an institution, cognitive frailty, Hgb, respiratory disease, renal insufficiency, diabetes, malignancy AUROC = 0.75, calibration: Visually OK Backward selection using AIC as criterion Bootstrap for internal validation Comments: Sound methodology, relatively small cohort from two centers
Menendez-Colino, et al[104] **Hip Int** **2020**	Cohort study Single center (La Paz University Hospital, Madrid, Spain) Jan 2013 – Feb 2014	n = 509 (include non-operated patients) Candidate risk factors: Patient demographics, Barthel Index, cognitive function, grip strength, BMI, comorbidities, biochemistry Outcome: 1-year mortality Statistics: Logistic regression, AUROC, H&L test, validation metrics compared with NHFS, CCI score, and ASA score	Overall 1-year mortality: 23.2% Risk factors included: Age, sex, Barthel, cognition, grip strength, BMI, heart disease, secondary hyperparathyroidism, hgb AUROC = 0.79, (AUROC for NHFS = 0.66, CCI score = 0.61, and ASA score = 0.60) Calibration: H&L test all show $p > 0.05$ Comments: Comparison of the new score with the previous scores (i.e., comparing internal with external

			validation). Development and internal validation performed on the same data
Huette, et al[212] **Sci Rep** **2020**	Cohort study Single center (Amiens University Hospital, France) June 2016 - June 2017	n = 309 Candidate risk factors: Patient demographics, BMI, comorbidities, comedication, smoking, LEE score (CV risk), ADL function, biochemistry, procedure type, anesthesia type, surgical delay, LOS Outcome: 1-year mortality Statistics: t-test of proportions, Cox regression, Kaplan-Meier curves	Overall 1-year mortality: 23.9% Risk factors found: Age, surgical delay, LEE score Comments: Imprecise estimates, no prediction modeling – only evaluation of risk factors
Kimura, et al[213] **J Orthop Surg** **2019**	Cohort study Northern Kyushu District, Japan (17 hospitals) March 2013 – March 2016	n = 517 (20 lost to follow-up) Candidate risk factors: Patient demographics, BMI, comorbidities (CCI), alcohol, smoking, BMD, osteoporosis treatment, surgical delay, fracture type, procedure type, Barthel index, LOS, discharge destination Outcome: 1-year mortality (from discharge) through telephone interview with patient or relatives Statistics: Kaplan-Meier, Cox regression	Overall 1-year mortality: 9.1% Risk factors found: Males: Previous vertebral fractures and low Barthel Index. Females: BMI, CCI, smoking, LOS < 14 days, low Barthel index Comments: Low overall mortality – possibly due to exclusion of in-hospital mortality and long hospital stays
Bülow, et al[214] **Bone Joint J** **2019**	Cohort study Swedish arthroplasty register 2005 – 2012	n = 42,354 (arthroplasties for a femoral neck fracture) Candidate risk factors: CCI score, Elixhauser Comorbidity Score, age, sex Outcome 30-day to 5-year mortality Statistics: Kaplan-Meier, Cox regression, AUROC	Overall 5-year mortality: 48% Dose-response like association between both indices and mortality 1-year AUROC < 0.6 for crude models, < 0.7 for models including age and gender

			Time-dependent AUROC: Slowly declining discrimination with increasing follow-up time Comments: Large study, sound methodology, not all fracture patients included – only patients receiving arthroplasties
Bliemel, et al[115] **Int Orthop** **2017**	Cohort study Single center (University Hospital Marburg, Germany) April 2009 – September 2011	n = 402 (90 lost to follow-up) Candidate risk factors: Comorbidities: Neurological (including stroke), cardiovascular, respiratory, gastrointestinal, kidney/urinary tract, musculoskeletal Outcome: In-hospital and 1-year mortality Statistics: Proportions overall and among patients with/without the risk factors, group comparisons with Fisher's exact test	Overall 1-year mortality 27% Risk factors found: Neurological, respiratory, gastrointestinal, and urinary tract disorders Comments: Crude estimates; no adjustment for confounders, unspecific exposure categories (organ system) including diseases with varying prognosis
Bliemel, et al[215] **Osteoporos Int** **2016**	Cohort study Single center (University Hospital Marburg, Germany) April 2009 – September 2011	n = 402 (11 lost to follow-up) Candidate risk factors: Patient demographics, fracture type, procedure type, ASA score, self-reported quality of life (EQ-5D), Barthel index, comorbidities (CCI), MMSE Statistics: Logistic regression, AUROC, H&L test	Overall 1-year mortality: 28.1% Risk factors included: ASA score, EQ-5D, sex, MMSE AUROC: 0.74, H&L test not significant Comments: Development and validation performed on the same sample
Cenzer, et al[107]	Cohort study Health and retirement study (USA) 1992 - 2010	n = 857 Candidate risk factors: 34 variables from the following domains: Demographics, socioeconomic status, comorbidities, geriatric symptoms, and function	Overall 1-year mortality: 27% Risk factors included: Age, sex, heart failure, difficulties preparing meals, unable to drive AUROC: 0.72, calibration presented in a table.

		Statistics: Best-subsets regression, bootstrap validation, optimism-corrected AUROC	Comments: Methodology sound, relatively small sample and the cohort is relatively old
Adunsky, et al[216] Aging Clin Exp Res 2012	Cohort study Single Center (Chaim Sheba Medical Center, Israel) 1999 - 2008	n = 1,114 Candidate risk factors: AF (divided into paroxysmal AF and Chronic AF), patient demographics, comorbidities Outcome: 30-day, 90-day, and 1-year mortality Statistics: Cox regression, survival curves based on the regression analysis	1-year mortality: 9.8% (sinus rhythm), 11.5% (paroxysmal AF), and 20.3% (Chronic AF) Risk factors found: AF, age, sex, diabetes Low mortality – selection bias? (16% of patients excluded) Comments: No validation metrics reported
Wiles, et al[102] Br J Anaesth 2011	Cohort study Nottingham University Hospitals May 1999 – April 2009	n = 6,202 Candidate risk factors: NHFS (age, sex, cognitive score on admission, nursing home residency, number of comorbidities, malignancy, hemoglobin on admission), surgical delay Statistics: Kaplan-Meier curves among patients with NHFS ≤ 4 and > 4	1-year mortality overall: 29.3% 1-year mortality NHFS ≤ 4: 15.9%, NHFS > 4: 45.5% No clear effect modification from surgical delay Comments: No validation metrics reported
Kannegaard, et al[217] Age Ageing 2010	Cohort study Danish health registries Jan 1999 – Dec 2002	n = 42,076 Candidate risk factors: Patient demographics, comorbidities, comedications Statistics: Cumulative mortality, Cox regression	1-year mortality for women: 26.4%, for men: 37.1% Risk factors found: Age, sex, liver disease, renal disease, cancer, dementia, COPD, heart failure, medication related to the nervous system and digestive system/diabetes Comments: No validation metrics reported
Bellelli, et al[218]	Cohort study	n = 211 Candidate risk factors: Dementia, depression	1- year mortality: 8% Risk factors found: Depression, dementia

Int J Geriatr Psychiatry 2008	Rehabilitation unit, Brescia, Italy Jan 2002 – April 2006	Statistics: Kaplan-Meier, Cox regression	Increased mortality among double exposed Comments: Imprecise estimates, low overall mortality (follow-up start at discharge from rehabilitation unit)
Jiang, et al[182] J Bone Miner Res. 2005	Cohort study Capital Health region, Edmonton, Alberta, Canada March 1994 – Feb 2000	n = 3981 Candidate risk factors: Patient demographics, comorbidities Statistics: Logistic regression, AUROC, H&L test, Geographical split validation	Overall 1-year mortality: 30.8% Risk factors included: Age, sex, nursing home residency, COPD, pneumonia, CVD, CKD, cancer, heart failure, malnutrition, electrolyte disorder AUROC: 0.74, H&L test: Insignificant p-value Comments: 1-year mortality from discharge. In this light, mortality seems high – old data? Otherwise sound methodology
Franzo, et al[219] Eur J Epidemiol. 2005	Cohort study Friuli Venezia Giulia region, Northeast Italy 1996 - 2000	n = 6,629 Candidate risk factors: Patient demographics, comorbidities, surgery delay, hospital volume Statistics: Logistic regression (non-conditional and multilevel models)	Overall 1-year mortality: 25.3% Risk factors found: Age, sex, high hospital surgical volume, surgical delay (not in multilevel models) Comments: No validation metrics reported

Abbreviations: ADL: Activities of daily living, AF: Atrial fibrillation, AIC: Akaike's information criterion, ASA: American Society of Anesthesiology, AUROC: Area under the receiver-operating characteristics curve, BMD: Bone mineral density, BMI: Body Mass Index, CCI: Carlson's Comorbidity Index, CVD: Cardiovascular disease, CKD: Chronic kidney disease, H&L: Hosmer & Lemeshow (goodness of fit), LOS: Length-of-stay, MMSE: Mini mental state examination, NHFS: Nottingham Hip Fracture score

Table S3. Schematic overview of most important previous prediction models for mortality tested on a cohort of patients with hip fracture

Study II: Prediction of postoperative mortality – previous prediction models					
Model name	Follow-up time	N	Included predictors	Validation technique	Validation metrics
Almelo Hip Fracture Score[220]	30 days	850	Age, sex, hemoglobin, cognitive score, malignancy, independent living, number of comorbidities, mobility, ASA score	Development and validation on the same sample	Int. val: AUC = 0.82 H&L test: NS
American Society of Anesthesiology (ASA) score[104,106]	6 months 1 year	509, 481		Development and validation on the same sample	Ext val: AUC range: 0.60 – 0.66 H&L test: NS
Brabant Hip Fracture Score (BHFS)[105]	30 days 1 year	925	Age, sex, nursing home residency, hemoglobin, respiratory disease, diabetes, malignancy	Bootstrapping	Int. val: AUC range: 0.71 - 0.75 H&L test: NS
Charlson Comorbidity Index (CCI)[103,104,201,214,221]	30 days, 90 days, 6 months 1 year, 2 years, 5 years	509, 42354, 195, 1050, 31443	Age, sex + CCI variables	Split sample, bootstrapping	Ext val: AUC range: 0.61 – 0.79 H&L test: NS

Elixhauser Comorbidity Index[201,214]	30 days, 90 days, 1 year, 2 years, 5 years	42354, 31443	Age, sex + Elixhauser variables	Bootstrapping	Ext val: AUC range: 0.66 – 0.72
Estimation of physiologic ability and surgical stress (E-PASS)[221]	30 days	1050	Age, severe heart disease severe pulmonary disease, diabetes. performance status, ASA score, intraoperative blood loss, operation time, extent of skin incision	Validation only	Ext val: AUC = 0.72 H&L test: NS
Health and retirement study[107]	1 year	857	Age, sex, heart failure, difficulties preparing meals, unable to drive	Bootstrapping	Int. val: AUC = 0.73 Calibration inspected in table
Hip fracture estimator of mortality Amsterdam (HEMA)[222]	30 days	1050	Age, in-hospital fracture, malnutrition, myocardial infarction, heart failure, pneumonia, renal failure, malignancy, serum urea > 9 mmol/L	Split sample	Int. val: AUC = 0.79 H&L test: NS
Hip-Multidimensional Frailty Score[106]	6 months 1 year	481	Sex, serum albumin, mid-arm circumference, CCI, walking dependency, cognitive function, risks of falling, nutritional status	Development and validation on the same sample	Int. val: AUC = 0.78 Calibration not reported

HULP-HF[104]	1 year	509	Age, sex, Barthel index, cognitive score, grip strength, BMI, CVD, HPT (vit. D ass.), hemoglobin	Development and validation on the same sample	Int. val: AUC = 0.79 H&L test: NS
Jiang et al (no name)[182,221]	In-hospital 1 year	3981, 1050	Age, sex, nursing home residency, COPD, pneumonia, CVD, CKD, cancer, heart failure, malnutrition, electrolyte disorder	Split sample	Int. val: AUC range: 0.74 - 0.82 H&L test: NS Ext. val: AUC = 0.78 H&L test: p = 0.04
National Hip Fracture Database (UK)[223]	30-day	7905	Age, sex, ASA score, physical status grade, ability to walk indoors, fracture type, admission from own home	Split sample	Int. val: AUC = 0.71 H&L test: NS
National in-patient sample database (USA)[224]	In-hospital	535475	Age, sex, surgery delay, heart failure, pulmonary circulation disease, renal failure, weight loss, fluid/electrolyte disorders	Split sample	Int. val: AUC = 0.74 H&L test: NS
Nottingham Hip Fracture score (NHFS)[103,106,220,221,223,225-227]	30 days 6 months 1 year	850, 481, 195, 7905, 997, 9017, 1050	Age, sex, hemoglobin, cognitive score, malignancy, independent living, number of comorbidities	Split sample	Int. val: AUC = 0.72 H&L test: NS Ext val: AUC range: 0.66 – 0.78 H&L test: NS

Possum, O-Possum, P-Possum[103,221,225]	30 days 6 months 1 year	195, 1050, 997	Age, cardiac signs, respiratory signs, SBP, pulse rate, GCS, Serum Urea, Serum Na, Serum K, Hemoglobin, white blood cell count, ECG, operative magnitude, number of operations in 30 days, blood loss, contamination, presence of malignancy, timing	Split sample	Ext val: AUC range: 0.66 – 0.77 H&L test: NS
Sanz-Reig, et al (no name)[228]	In-hospital	331	Age, sex, heart failure, asthma, rheumatologic disease, lung cancer, platelet inhibitors	Development and validation on the same sample	Int. val: AUC = 0.77 H&L test: NS
Surgical Outcome Risk Tool[226]	30 days	9017	Age, ASA score, malignancy, urgency of surgery, severity of surgery, high risk specialty	Split sample	Ext val: AUC = 0.70 H&L test: NS

This list includes the most important scores and validation work performed. For a complete list of papers developing and validating the different scores, please see the systematic review by Marufu et al[101].
Abbreviations: Abbreviations: AUC: Area under the receiver-operating characteristics curve, BMI: Body Mass Index, CVD: Cardiovascular disease, CKD: Chronic kidney disease, COPD: Chronic obstructive pulmonary disease, ECG: Electrocardiogram, Ext. val: External validation, GCS: Glasgow Coma Score, H&L: Hosmer & Lemeshow (goodness of fit), HPT: Hyperparathyroidism, Int. val: Internal validation, SBP: Systolic blood pressure.

Table S4. Papers relevant for Study III. Listed papers report on prefracture stroke as a risk factor for postoperative mortality

Study III: Interaction effect of stroke history and hip fracture on postoperative mortality			
Author, Journal, Year	**Design, setting, period**	**Study population, exposure, outcome**	**Results, comments**
Bliemel, et al[115] **Int Orthop** **2017**	Cohort study Single center (University Hospital Marburg, Germany) April 2009 – September 2011	n = 402 (90 lost to follow-up) Exposure: Baseline medical conditions (neurological (including stroke), among others) Outcome: In-hospital and 1-year mortality Statistics: Counts and proportions overall and among patients with/without the exposure, group comparisons using Fisher's exact test	Overall in-hospital and 1-year mortality of 6% and 27% Mortality increased to 8% and 37% among patients with neurological comorbidity Comments: Crude estimates. Not adjusted for potential confounders, unspecific exposure categories (organ system), which includes different diseases with varying prognosis
Nho, et al[111] **J Orthop Sci** **2014**	Medical record review Soonchunhyang University Hospital, South Korea May 2003 – Dec 2008	n = 548 Exposure: Stroke history (n = 77) Outcome: 1-year mortality Statistics: Logistic regression (crude and adjusted)	Overall 1-year mortality 12.2% No increased 1-year mortality among stroke patients Comments: Adjusted logistic regression point to an association, but CIs are very wide. Authors conclude no association, no mention of potential power problems
Fisher, et al[110] **Stroke Res Treat** **2013**	Cohort study Single center (Canberra Hospital, Australia) Unknown study period	n = 761 Exposure: Stroke history (n = 100) Outcome: In-hospital mortality Statistics: Logistic regression (adjusted for age and sex)	In-hospital mortality 5% vs 4.8% in prefracture stroke vs non-stroke patients No association in logistic regression (OR 1.07) Comments: Imprecise estimates

Feng, et al[114] **Clin Orthop Relat Res** **2009**	Medical record review Xuanwu Hospital, Beijing, China Jan 2000 – May 2006	n = 1,379 Exposure: Patients stratified on poststroke hemiplegia. Risk factors for mortality Outcome: 1-year mortality Statistics: Logistic regression	1-year mortality: 24.8% vs 10.8% in hemiplegic vs non-hemiplegic patients Risk factors among hemiplegic patients: ASA score, prefracture mobility, comorbidities, cognitive level Comments: Only crude estimates for mortality, narrow definition of stroke (only hemiplegia)
Penrod, et al[113] **J Gerontol A Biol Sci Med Sci** **2008**	Three US cohorts (pooled data) Mount Sinai cohort (n = 1177, age 50+, New York City hospitals, Aug 1997 – Dec 1999) Baltimore Hip Studies cohort (n = 629, age 65+, Baltimore area hospitals, Jan 1990 – June 1991) Hospital for Joint Diseases cohort (n = 886, age 65+, New York City, 1987 – 2001)	n = 2,692 Exposure: Demographic factors and comorbidities Outcome: 6-month mortality Statistics: Logistic regression	Overall 6-month mortality: 12% Risk factors: Sex, ethnicity, age, dementia, cancer, COPD, and heart failure - but not stroke Comments: Relatively old data – treatment strategies might have changed, and prognosis improved. Selection bias in the cohorts?
Youm, et al[116] **J Orthop Trauma** **2000**	Hospital for Joint Diseases cohort New York, USA July 1987 – March 1997	n = 862 Exposure: Previous stroke Outcome: In-hospital and 1-year mortality Statistics: Logistic regression	In-hospital mortality: 1.6% vs 3% in prefracture stroke vs non-stroke patients 1-year mortality: 15.9% vs 10.6% in prefracture stroke vs non-stroke patients (OR 1.6) Comments: Imprecise estimates, patients with dementia excluded, old data
Ramnemark, et al[53]	Medical Record review	n = 568	Elevated mortality at all follow-up points (stroke

Stroke 2000	Umeå University Hospital, Sweden Admissions during 1980, 1983, 1987, 1993, and 1997	Exposure: Previous stroke Outcome: 30-day, 1-year, and 5-year mortality Statistics: Comparison of proportions, Kaplan-Meier statistics	vs non-stroke): 8.8% vs 3.3%, 29.3% vs 16.8%, 80.3% vs 59.7% at 30 days, 1 year, and 5 years Comments: Only crude estimates

Abbreviations: COPD: Chronic obstructive pulmonary disease, LOS: Length-of-stay, OR: Odds ratio

Table S5. Papers relevant for Study IV. Listed papers report on incidence of second hip fracture among patients with hip fracture and risk factors associated with an increased risk of this outcome

Study IV: Prefracture stroke history and the risk of recurrent fracture			
Author, Journal, Year	**Design, setting, period**	**Study population, exposure, outcome**	**Results, comments**
Helynen, et al[229] **Arch Orthop Trauma Surg** **2022**	Cohort study Oulu University Hospital, Finland 2013 - 2016	n = 1130 Exposure: Patient demographics, biochemistry, mobility, FRAX tool, BMD Outcome: Second hip fracture Statistics: Correlation analysis, Between-group comparisons (Kruskall Wallis, t-test, or ANOVA)	11.3% of patients were admitted with a second hip fracture Risk factors: Female sex, low BMD, high FRAX score, poor mobility, low calcium Comments: Competing risk of death not considered, complete case analysis with many missing values
Larrainzar-Garijo, et al[121] **Arch Orthop Trauma Surg** **2021**	Cohort study 45 hospitals in 15 different regions of Spain June 2014 – June 2016	n = 994 with incident hip fracture Exposure: Patient demographics, comorbidities, prefracture mobility Outcome: Second fracture, mortality Statistics: Comparison of baseline characteristics. Cox regression for mortality	10.2% with a second fracture Risk factors for second fracture: History of falls and fractures, dependent outdoor walking Increased mortality among patients with second fracture

			Comments: Crude, descriptive statistics only (for risk factors for second fracture). Methodology difficult to understand
Khalid, et al[128] **J Bone Miner Res.** **2021**	Cohort study Three distinct cohorts: SIDIAP, Spain, 2006 – 2016 CPRD, England, 1995 – 2018 DHR, Denmark, 1995 – 2016	SIDIAP database used for development of prediction model, n = 35,526 Other cohorts used for validation Exposure: Incident fracture Outcome: New fracture (hip or any osteoporotic fracture) LASSO regression used for variable selection, logistic regression for final model	Second hip fracture 1- and 2-year proportions: SIDIAP: 0.84% and 1.69%, CPRD: 7.3% and 8.25%, DHR: 2.96% and 4.46% Risk factors for new hip or osteoporotic fracture: age, sex, PPI use, dementia, type II diabetes Comments: No mention of how competing risk of death is handled
Sheikh, et al[122] **Eur J Orthop Surg Traumatol** **2019**	Cohort study Data from Leeds Teaching Hospital, reported to the National Hip fracture Database, England Sep 2008 – March 2011	n = 1,242 Exposure: Baseline characteristics Outcome: Second hip fracture within 2 years Statistics: Comparison of baseline variable between groups. Cox regression including all variables with different distribution between groups	66 patients had a second hip fracture during follow-up Risk factors: Increasing CCI, acute chest infection or urinary tract infection during index admission, dementia, pre-injury walking ability Comments: Competing risk of death not considered. Age and sex not included in multivariate analysis
Harvey, et al[130] **ANZ J Surg** **2018**	Cohort study New South Wales, Australia Jan 2002 – Dec 2012	n = 24,500 Exposure: CCI comorbidities, poor vision, Parkinson's disease, osteoarthritis, alcohol misuse, obesity, malnutrition/cachexia Outcome: Second hip fracture within 3 years	Second fracture cumulative incidence: 2.9%, 4.6%, 6.1%, and 8.1% for 1, 2, 3 and 5 years Risk factors: Malnutrition/cachexia, dementia, heart failure, Parkinson's disease, stroke, osteoporosis.

		Statistics: Cumulative incidence (competing risk of death), competing risk regression	Comments: Exposures modeled as time dependent, no info on medication, stroke not mentioned in the discussion
Joeris, et al[230] **Geriatr Orthop Surg Rehabil** **2017**	Delphi survey International expert panel	25 participants invited, 12 replied Two-round Delphi process for identification of risk factors	Consensus on risk factors: Fall/fracture history, osteoporosis, no osteoporosis treatment, impaired vision/missing vision aids, deteriorated mental or general health status, residential status, medication
Shen, et al[129] **J Am Med Dir Assoc** **2014**	Cohort study Taiwan National Health Insurance Research Database (NHIRD) Jan 2004 – Dec 2010	n = 90,314 with incident hip fracture Exposure: Baseline characteristics, comorbidities, medication use Outcome: Second hip fracture Statistics: Descriptive, proportions of second fractures, Kaplan-Meier estimates, logistic regression	Proportion of second fractures: 9.2% Risk factors: Age, sex, diabetes, obesity, hypertension, hyperlipidemia, stroke, low vision, bisphosphonates, steroids, paracetamol, NSAIDs, COX-2 inhibitors Comments: Patients aged 45+ years, competing risk of death not considered
Omsland, et al[231] **Bone** **2013**	Cohort study Norway 1999 - 2008	n = 81,867 Exposure: Age and sex Outcome: Second hip fracture Statistics: Cumulative incidence (competing risk of death), competing risk regression	1- and 2-year cumulative incidence: 4.4% and 6.9% (women) and 3.2% and 5.0% (men) Risk factors: Male sex and higher age (women only) Comments: No baseline characteristics presented, other factors such as comorbidities and medication could have improved the study
Ryg, et al[120] **J Bone Miner Res.** **2009**	Cohort study Danish Health registries 1977-2001	n = 169,145 with incident hip fracture. Incidences compared with age and sex-matched background population.	1- and 5-year cumulative incidence: 9% and 20% Risk factors: Age, sex, alcoholism, prior fracture, living alone, higher income

		Exposure: Baseline characteristics, comorbidities, medication use. Outcome: Second hip fracture within 1-5 years Statistics: Cumulative incidence (Kaplan-Meier), Cox regression	Comments: Competing risk of death not considered. Very high incidences compared to other studies
Lönnroos, et al[123] **Osteoporos Int** **2007**	Cohort study Central Finland Health Care registries and hospital medical records. 2002 - 2003	n = 501 with incident hip fracture. Exposure: Baseline characteristics, comorbidities, medication use Outcome: Second hip fracture Statistics: Cumulative incidence (Kaplan-Meier), Cox regression	1- and 2-year cumulative incidence: 5.1% and 8.1% Increase in psychotropic drug use from first to second fracture Comments: Competing risk of death not considered. Insufficient power to detect risk factors through Cox regression
Berry, et al[124] **Arch Intern Med** **2007**	Cohort study Framingham Heart study 1952 - 2003	n = 481 with incident hip fracture Exposure: Baseline characteristics Outcome: Second hip fracture Statistics: Cumulative incidence, Cox regression	1-, 3- and 5-year cumulative incidence: 2.5%, 5.7% and 8.2% Risk factors: Age and functional status Comments: Imprecise estimates due to low power
Yamanashi, et al[125] **Osteoporos Int** **2005**	Cohort study 4 Japanese hospitals Jan 1996 – Dec 1999	n = 714 with incident hip fracture Exposure: Baseline characteristics and comorbidities Outcome: Second hip fracture Statistics: Cumulative incidence (Kaplan-Meier), logistic regression	1-, 2- and 3-year cumulative incidence: 3.8%, 6.6% and 8.4% Risk factors: Dementia, Parkinson's disease Comments: Competing risk of death not considered, imprecise estimates due to low power
Charpulat, et al[126] **Osteoporos Int**	Cohort study	n = 632 women with incident hip fracture	Average incidence of 2.3% per year

2003	Study of Osteoporotic Fractures, USA 1986 - 1988	Exposure: Baseline characteristics, risk factors for osteoporosis Outcome: Second hip fracture Statistics: Cumulative incidence (Kaplan-Meier), logistic regression	Protective factors: Daily exercise, normal vision, HRT Risk factors: Weight loss since youth, low BMD Comments: Competing risk of death not considered Old data

Abbreviations: BMD: Bone mineral density, CCI: Charlson Comorbidity Index, CPRD: UK Clinical Practice Research Datalink, DHR: Danish Health Registries, HRT: Hormone replacement therapy, SIDIAP: Catalan Information System for Research in Primary Care.

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13. Appendices

Appendix I

Paper I

Appendix II

Paper II

Appendix III

Paper III

Appendix IV

Paper IV

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