UiT The Arctic University of Norway

Faculty of Health Sciences

Department of Clinical Medicine

Secondary Fracture Prevention and Forearm Fracture Epidemiology

NoFRACT – The Norwegian Capture the Fracture Initiative

Camilla Andreasen

A dissertation for the degree of Philosophiae Doctor, August 2023

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Acknowledgements

When applying for the position as a PhD student on the NoFRACT project, I wrote that being challenged in my job is one of my key motivators. This PhD has definitely challenged me, and I have learned more than I could ever have hoped for.

First, I would like to thank my principal supervisor Åshild Bjørnerem. When I first got a position in Tromsø, the chief of the department warned me about the forces of nature in North Norway, and the weather in Tromsø is at times powerful. However, I think you are the greatest force of nature I have met in Tromsø. Åshild, you are energetic as few, optimistic, unstoppable and your support has been never-ending. Working with you have taught me so much, your sense of structure, eye for details and sharp mind has challenged me and made me a much better researcher. I have enjoyed your positive spirit, your eagerness to move forward and I am grateful that you recruited me to the NoFRACT project. Thank you.

A hearty thanks goes to my co-supervisors; Cecilie Dahl, Torbjørn Wisløff and Tone Kristin Omsland. Cecilie, thank you for teaching me to speak STATA, for your patience, optimism, your fast and always helpful replies to my never-ending stream of emails. Thank you, Torbjørn for your impressive statistical knowledge and always sharp comments. Tone, I have truly enjoyed working with you. Your calm nature, scientific mind and support has been precious.

Tove Tveitan Borgen, thank you for always being supportive. You must be the definition of a good colleague: reliable, a good scientist, great company and hard working. Lene Bergendal Solberg, thank you for all the support in writing articles, your constructive feed-back and your ability to pin-point the central parts are inspiring. I am grateful to all my co-authors for their engagement in the NoFRACT project; Trude Basso, Gunhild Hagen, Ellen Apalset, Jan-Erik Gjertsen, Wender Figved, Lars Hübschle, Jens-Meinhard Stutzer, Ida Lund, Ann Kristin Hansen, Frida Igland Nissen, Jan Elvenes, Ragnar Martin Joakimsen, Unni Syversen, Erik Fink Eriksen, Lars Nordsletten and Frede Frihagen. It has not always been easy to manage inputs from so many co-authors, but at the same time the collaboration in NoFRACT has energized me. I am thankful for all your comments in manuscripts, encouraging emails and for cheering me on.

Thank you to Marit Osima, Kjerstin Aune, May Greta Pedersen, Anita Kanniainen for working together with me on NoFRACT at the Clinical Research Unit in Tromsø. Thank you for welcoming me and teaching me the clinical aspects of the fracture liaison service work.

I would also like to thank my former colleagues at Department of Medicine, University Hospital of North Norway; Julia, Ieva, Maren, Ingvild, Linn, and Caroline for welcoming me to Tromsø. Thank you for all the good memories, support, knitting-nights and for great company on hikes.

Lastly, I would like to thank my family and friends for their love and support. A special thanks to my mum, my dad, Emma, Lasse, Julie, and Sara knowing that you are always there means the world to me.

Til Nis, Ásla og Ingvild - Tak for hverdagen, for oplevelserne og det hjem I giver mig. I er mit nordlys i mørketiden, mit det allerbedste.

Camilla Andreasen

Nuuk, Greenland. August XX, 2023.

Funding

The Norwegian Capture the Fracture Initiative project was supported with grants from; The Regional Health Authorities, grant number 243852; Northern Norway Regional Health Authority, grant number 14083; Vestre Viken Hospital Trust, grant number 19003007; St. Olavs University Hospital, grant number 46055600-51; and by South-Eastern Norway Regional Health Authority, grant number 2017032.

Abbreviations

AOD	Anti-Osteoporotic Drug
BMD	Bone Mineral Density
BMI	Body Mass Index
CI	Confidence interval
CTX	C-terminal telopeptide of type I collagen
DAG	Directed acyclic graphs
DXA	Dual-energy X-ray Absorptiometry
EU	European Union
FLS	Fracture Liaison Services
FRAX	The Fracture Risk Assessment Tool
HR	Hazard Ratio
ICD-10	International Classification of Disease 10^{th} revision codes
IOF	International Osteoporosis Foundation
MOF	Major osteoporotic fracture
NCSP	NOMESCO surgical procedure codes
NHNV	Non-hip-non-vertebral
NoFRACT	Norwegian Capture the Fracture Initiative
NOMESCO	Nordic Medico-Statistical Committee
NOREPOS	Norwegian Epidemiologic Osteoporosis Studies
NPR	Norwegian Patient Registry
P1NP	Propeptide of type 1 procollagen
PAS	Patient administrative register
PPV	Positive predictive value
PY	Person-years
SD	Standard deviations
SW-CRT	Stepped-wedge cluster-randomized trial

Summary

Background: Osteoporosis and fragility fractures are common, and a burden to the society. Anti-osteoporotic drugs (AODs) that reduce the risk of future fracture are available, still, less than 20% of fragility fracture patients receive AODs. Fracture Liaison Services (FLS) are proposed as a solution for closing this treatment gap. We studied the effect on a standardised FLS on rates of subsequent fragility fracture and all-cause mortality. We investigated the nationwide age-standardised incidence rates of forearm fractures in women and men over 20 years of age between 2008 and 2019 in Norway.

Methods: Paper I and II: A stepped-wedge cluster-randomised trial at seven Norwegian hospitals. The hospitals were randomised in three clusters. The intervention went from May, 2015 – Dec, 2018. Patients over 50 years with a low-energy fracture were invited to the FLS intervention. The intervention included assessment and treatment of osteoporosis, if indicated. Analyses were based on national register data on all patients aged 50-99 years with an index fracture during 2011-2018. Participants were included in the analyses regardless of exposure to the intervention. Paper III: Analyses were based on all forearm fractures treated at Norwegian hospitals from Jan 1, 2008, to Dec 31, 2019.

Results: Paper II: The standardised FLS reduced the risk of subsequent fragility fractures by 12%, subsequent hip fracture by 24% and, mortality by 26% after the first fracture in both women and men. The study included 57,186 patients in the control group and 47,071 patients in the intervention group. Paper III: The mean annual incidence rate per 100,000 PY was 565 in women and 231 in men in 2008-2019. The age-adjusted incidence rates of distal forearm fractures declined slightly during the study period. The study included 181,784 forearm fractures in 45,628,418 person-years (PY).

Conclusion: The FLS reduced the risk of subsequent fragility fractures and mortality. The high incidence of forearm fractures in Norway warrants attention. Preventive measures and implementation of FLSs in all orthopaedic departments could be a solution.

List of papers

The thesis is based on the following papers.

Paper I

Andreasen C, Solberg LB, Basso T, Borgen TT, Dahl C, Wisløff T, Hagen G, Apalset EM, Gjertsen JE, Figved W, Hübschle LM, Stutzer JM, Elvenes J, Joakimsen RM, Syversen U, Eriksen EF, Nordsletten L, Frihagen F, Omsland TK, Bjørnerem Å. Effect of a Fracture Liaison Service on the Rate of Subsequent Fracture Among Patients With a Fragility Fracture in the Norwegian Capture the Fracture Initiative (NoFRACT): A Trial Protocol.

JAMA Netw Open. 2018 Dec 7;1(8):e185701. doi: 10.1001/jamanetworkopen.2018.5701.

Paper II

Andreasen C, Dahl C, Frihagen F, Borgen TT, Basso T, Gjertsen JE, Figved W, Wisløff T, Hagen G, Apalset EM, Stutzer JM, Lund I, Hansen AK, Nissen FI, Joakimsen RM, Syversen U, Eriksen EF, Nordsletten L, Omsland TK, Bjørnerem Å, Solberg LB. Fracture Liaison Services and Subsequent Fracture Risk: a multicentre, pragmatic, Stepped-Wedge Cluster-Randomized controlled trial.

Submitted to Nature Medicine on August 21, 2023.

Paper III

Andreasen C, Dahl C, Solberg LB, Borgen TT, Wisløff T, Gjertsen JE, Figved W, Stutzer JM, Nissen FI, Nordsletten L, Frihagen F, Bjørnerem Å, Omsland TK. Epidemiology of Forearm Fractures in Women and Men in Norway 2008-2019.

Submitted to Osteoporosis International on March 27, 2023. Currently under review.

1 Background

1.1 Definition of osteoporosis and fragility fractures

The World Health Organization defines osteoporosis as a progressive systemic skeletal disease characterised by low bone mass and micro-architectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility of fracture.(1)

Since 1994, Bone Mineral Density (BMD) measured by Dual-energy X-ray Absorptiometry (DXA) scan has been the most common tool used for diagnosing of osteoporosis. The T-score refers to the number of standard deviations (SD) above or below the average BMD in premenopausal women. A BMD T-score at the femoral neck of -2.5 or less is defined as osteoporosis, a BMD T-score between -1 and -2.5 as osteopenia, and a BMD T-score above -1 is normal.(2) In the guidelines for endocrinologists in Norway, osteoporosis is diagnosed as either having had a low-energy fracture or a BMD T-score of -2.5 or below by DXA scan of the lumbar spine, femoral neck or total hip in individuals over 50 years of age.(3)

Osteoporosis weakens the bone and increase the risk of fracture, and the clinical consequence of osteoporosis is fragility fractures.(1) Fragility fractures are defined as fractures that occur spontaneously or after a minimal trauma that normally would not cause a fracture e.g., a fall from standing height or less.(4) The fractures related to low BMD are clinical vertebral fractures, fractures of the distal forearm, proximal humerus, clavicle, rib-sternum, pelvis-sacrum, and proximal femur.(5) Major osteoporotic fracture (MOF) is a cluster of the most common osteoporotic fractures; proximal femur, clinical vertebral fractures, proximal humerus, and distal forearm.(5)

1.2 Epidemiology of osteoporosis and fragility fractures

Osteoporosis is a major health issue. Every year osteoporosis causes more than 9 million fractures worldwide and is an extensive reason for fractures in adults over 50 years of age.(5, 6) The estimated prevalence is 6.6% for men and 22.1% in women older than 50 years in the European Union (EU).(7) These estimates are based on an assumption of similar mean femoral neck BMD across the EU, prevalence are calculated using the mean BMD of young, white adult women in the NHANES III study as reference population and data on demographics of each country).(7) In Norway, it is estimated that 240,000-300,000 Norwegians have osteoporosis, based on BMD measurements.(8, 9) Hip fractures accounts for most of the expenditures,

morbidity and mortality and can be used as a proxy for osteoporosis when comparing incidence of osteoporosis between countries.(7)

Fracture incidence is best documented for hip fracture and varies across the globe with the highest incidences in northern Europe.(10) This variation in incidence rates is most pronounced in younger age groups (under 65-70 years) and becomes smaller with increasing age.(11) Norway, as well as the rest of Scandinavia, has among the highest incidence rates of both forearm and hip fractures worldwide.(5, 12-14) The incidence rates of hip fracture in Scandinavia is 247-290 per 100,000 person-years (PY) for men and 539-574 per 100,000 PY in women.(13) Each year almost 10,000 Norwegians above the age of 50 years suffer a hip fracture(15) and the annually number of distal forearm fractures is estimated to constitute almost 14,000.(16) Hip fractures accounts for 20% of all fragility fractures,(17) implying 50,000 annual fragility fractures in Norway.

Secular trends for age- and sex standardised fracture incidence rates are poorly documented, except for hip fracture, which increased until 1980 and then plateaued or decreased over the last decades in many developed countries, especially in women.(6, 18-20) This is also seen in Norway; from 1999 to 2019 with a decline in the age-standardised hip fracture incidence rate of 27% in women and 20% in men. However, the total annual number of fractures decreased by 11% in women, but increased by 20% in men. Nevertheless, the total annual number of hip fractures has not declined, due to an increase in the numbers of elderly.(21)

In North American, Australian, and Scandinavian studies, age-adjusted incidence rates of distal forearm fractures have declined since the 1980s.(14, 18, 19, 22) In Norway, a decline was suggested in data from Akershus in 2007, when age-adjusted incidence rates of distal forearm fractures were significantly lower than rates from Oslo, Norway in 1998/99.(14, 23) The incidences of distal forearm fractures are mainly estimated from small studies. However, in one nationwide Norwegian study based on the Norwegian Patient Registry (NPR), the mean age- and sex-adjusted incidence rate of distal forearm fractures in adult over 18 years of age was 244 per 100,000 PY in Norway from 2009-2014.(16) Still, time-trends in forearm fractures have not been investigated on nationwide data in Norway. Neither has the validity and coverage of forearm fracture diagnosis in NPR. Time-trends in age-adjusted incidence of distal forearm fractures from Skåne, Sweden increased from 1999 to 2010 in two studies,(24, 25) but another study in the north-eastern part of Skåne showed decreasing age-adjusted incidence rates of distal forearm fractures from 2011 to 2016.(22) In Stockholm, Sweden the incidence rates of forearm fractures in children and people over 65 years of age decreased from 2004 to 2010.(26)

In Denmark, the incidence rate of distal forearm fractures declined from 1995 to 2010, but no change was seen from 2013 to 2019.(19, 27) Moreover, no change in incidence rates of distal forearm fractures was detected in Finland from 2015 to 2019.(28)

The synergy of an ageing population and osteoporosis is expected to become an economic burden to the society.(29) The number of fractures is expected to double, and the associated costs will increase over the next decades.(6) The forecasted increase in the population over 50 years in EU from 2010 to 2025 is expected to increase the number of fractures in Denmark, Sweden and EU by 30%, 26%, and 28%, assuming no change in age- and sex-specific fracture rates.(7) In Norway cost associated with hip fracture is estimated to increase 65% from 2020 to 2040.(30)

Most fractures appear in the elderly population above the age of 65 years, but 20% of fragility fractures in Sweden occur in non-retired population (50-65 years of age), which results in sick leave and loss of productivity.(5) In 2010, the direct cost (not including the value of quality-adjusted life years lost) of fragility fractures in the EU was estimated to €37 billion and the costs is expected to increase.(31, 32) Compared to other non-communicable diseases, osteoporosis has major impact on healthcare budgets. For comparison, coronary heart disease was estimated to cost €45 billion and cerebrovascular disease €34 billion in 2003 prices.(7) The exact cost of fragility fractures in Norway is unknown, but the total annual fracture cost in Sweden is estimated to 5,639 million Swedish crowns (SEK) constituting 3.2% of the total health costs and is projected to increase to 26,301 million SEK in 2050, if there will be no change in age-differentiated fracture risk.(33)

1.3 Risk factors for fragility fractures

Osteoporosis is a multifactorial disease with several risk factors for osteoporosis and fracture. However, osteoporosis is a “silent disease” and without symptoms until a fracture occurs.(29)

1.3.1 Bone mineral density

Measurement of BMD using DXA is the most common way to assess fracture risk and is used as a surrogate for bone strength.(34) The predictive value of BMD for fracture varies with age and fracture type, and is best at the site that is measured.(35) Per SD decrease in BMD measured at the femoral neck, the risk of any fracture increase 1.6 fold and the risk of hip fracture increase 2.6 fold.(35, 36) Measurements of BMD provides diagnosis, prognosis, and a baseline for treatment. However, low BMD does not cause fractures alone and solely using BMD as a

parameter for treatment initiation is problematic. For example, prior falls increase the risk of future fractures.(37) Furthermore, most fractures occur at a BMD above -2.5 and identical BMD T-score has different impacts on fracture risk for different age groups. Furthermore, fracture rates vary more between countries than can be explained by BMD alone.(10)

1.3.2 Age, sex, ethnicity, lifestyle, and other risk factors

Increasing age is a major risk factor for osteoporosis due to the age-related bone loss in women, the prevalence of osteoporosis in women is 6.3% for 50-54 year-olds and 47.2% among 80-84 year-olds.(32) For men the decrease in testosterone with increasing age also results in bone loss. (38) However, this effect is slower than in women.(38) The incidence of fragility fractures rise markedly with age, though the rates rise differently for different types of fractures.(7) Hip fractures is most common in women over 70 years and distal forearm fractures in women over 50 years.(14, 18)

Female sex is an important risk factor for osteoporosis. Women have smaller bone diameters and loose bone earlier than men, resulting in a higher risk of fracture.(39) The earlier bone loss in women is due to a substantial decrease in oestrogen related to menopause, and after menopause the oestrogen level is approximately 10% of that in premenopausal women.(40) Over-all, 61% of fragility fractures occurred in women; 70% of hip fractures, 80% of forearm fractures, 58% of vertebral fractures and 75% of humerus fractures in a review of the global burden of fragility fractures.(17) The lifetime risk of any type of low-energy fractures after 60 years of age was 44% in women and 25% in men after adjusting for competing risk of death.(41) The overall age-standardised hip fracture incidence and lifetime probability of hip fracture in men was half that of women.(7, 13) Furthermore, risk of subsequent MOF after the first MOF was 41% higher for women compared to men.(42)

The hip fracture risk varies worldwide and is highest in Scandinavia.(32) Caucasians have lower BMD on average than Africans, Hispanics and Latina-Americans.(43) Furthermore, in a cohort from United Kingdom (UK) hip fracture rates were 2.7 times higher in white men compared to black men, and five times greater in white women compared to black women. Hip fracture rates were about half in South Asian individuals compared white individuals. (44) A Norwegian study showed lower risk of hip fracture among both male and female immigrants in Norway compared to residents born in Norway, with the lowest risk in immigrants from southeast and central Asia.(45) The ethnic and genetic relationship with BMD is complex and involves both ancestry, lifestyle, social factors and comorbidities. BMD has a high heritability ranging from 50-85% and genome wide association studies have found many different loci associated with

BMD.(46) A first degree relative with osteoporosis is a risk factor for development of osteoporosis.(47)

Lifestyle also plays an important role for bone health. The association between body mass index (BMI) and fracture risk is complex, because of the interaction between BMI and BMD.(48) Low BMI increase the risk of fragility fractures and high BMI, up to a certain point, is suggested to be osteoprotective.(48) However, obesity is associated with an increase in the risk of fractures which can be explained by an increased risk of falls, as well as metabolic changes such as increased inflammation that has a negative effect on bone.(49) Furthermore, taller people have on average higher risk of fragility fracture than shorter,(50) because longer and wider bones have a relative thinner cortex and higher cortical porosity.(51)

Physical activity has an important and positive effect on the skeleton in post-menopausal women, and improve bone mass, bone microarchitecture, muscle strength and balance, which will reduce the risk of falls.(52, 53) The reduction in falls is important because prior falls increase the risk of future fractures.(37) High alcohol intake and smoking, or any type of tobacco, also increase the risk of fracture.(54, 55) Risk factors for osteoporosis such as smoking, physical inactivity and diabetes are more common in those with social disadvantages.(43) In a Danish population-based study, social determinants as marital status, area of residence and income were strongly associated with fragility fractures, without any secular trends in these associations.(56)

Several diseases are associated with increased risk of osteoporosis and fracture, such as diabetes, rheumatoid arthritis, chronic obstructive pulmonary disease, and inflammatory bowel disease.(57) This is due to inflammation, hormonal effects, intestinal malabsorption, renal disease, or vitamin D deficiency.(57) Glucocorticoid and other medication can also cause osteoporosis, e.g. aromatase inhibitors, androgen deprivation agents, some anticonvulsants, proton pump inhibitors and selective serotonin receptor inhibitors.(58)

1.4 Fracture risk assessment

Among several fracture risk assessment tools, The Fracture Risk Assessment Tool (FRAX) is the most commonly used.(10) FRAX is a web-based algorithm (http://www.shef.ac.uk/FRAX) that calculate 10-year probabilities for MOF and hip fracture, by taking into account age, sex, BMI, previous fracture, and several other validated clinical risk factors for fracture. FRAX includes the competing risk of death and can be calculated without or with BMD, but with

higher accuracy of predicting future fractures if BMD is included.(59) FRAX was introduced in 2008 and country-specific models are now available, free online, for 78 countries. FRAX is incorporated into over 80 guidelines worldwide and cover 80% of the world's population.(60, 61) As with any other algorithm the current version of FRAX has limitations. It does not consider dose-response of several risk factors. FRAX work dichotomously even though it is well known that the risk of fracture increase with increased exposure of e.g., number of previous fractures, and amount of smoking, alcohol intake, and glucocorticoids. Furthermore, the history of falls is not included in the model.(32) A fall predicts future falls and is a risk factor for future fractures independently of the FRAX score.(62) Femoral neck is always used as the site of BMD, even if lumbar spine BMD is lower and implies a higher risk of fracture. However, a new version of FRAX, FRAXPlus, has recently been developed and designed to account for several of these limitations. In this new model, the risk of hip fracture and MOF is adjusted according to 0, 1, 2 or ≥3 falls in the past year. Furthermore, in FRAXPlus the risk according to site of recent fracture, type 2 diabetes, high dose of glucocorticoids, and measurements of trabecular bone score and lumbar spine BMD can be added to the algorithm. However, it is made clear on the website that there currently is no available evidence for the accuracy of the multiple adjustments, and FRAXPlus is not free. Although high FRAX-scores and low BMD T-scores are clearly associated with increased risk of fracture, most fractures are still not identified by these scores.(63) And the risk of fragility fractures is often underestimated, mostly so in those with the highest risk of fracture according to FRAX.(64)

1.5 Risk of subsequent fracture, morbidity, and mortality

Fragility fractures result from a combination of bone fragility and falls. A prior fractures is one of the most important risk factors for future fractures and the risk of future fractures doubles after the first fracture.(42, 65-67) Furthermore, a hip fracture increase the risk of a new hip fracture three times.(11) The risk of subsequent fractures is imminent and wanes progressively over time, but never return to the level before the fracture.(42, 61, 66, 68-70) In an Icelandic cohort, 45% of individuals who suffered subsequent fractures did so within the first year.(61) In a Danish cohort of hip fracture patients 28% had suffered a MOF in the preceding 10 years, the most common type of MOF was distal forearm and humerus fracture (over 70%).(71) In the Norwegian Epidemiologic Osteoporosis Studies (NOREPOS) study, the ten-year risk of a second hip fracture was 15% for women and 11% for men, after a first hip fracture, with a

median time to the second hip fracture of 1.5 year. In total, 75% of all new hip fractures occurred within the next 5 years.(70)

Musculoskeletal diseases have the fourth greatest impact on the health, affecting 6.8% of the world population.(72) Fractures increase both the risk of subsequent fractures, morbidity, and mortality.(72) Fractures lead to acute pain, hospitalisation, and recovery can be slow and incomplete. Hip, vertebral and distal forearm fractures result in substantial loss in health related quality of life and this reduction last for at least 18 months for hip and vertebral fractures.(73) Hip and vertebral fractures have the greatest impact on daily activities, but nearly half of patients with distal forearm fractures report unsatisfactory function after 6 months.(61, 74) Risk of institutionalising six months after hip fractures was 14.9 and 11.2 per 100 women and men. The risk was similar for pelvis and vertebral fractures. Relative risk of institutionalisation was 0.80 and 0.68 for proximal humerus fracture, 0.46 and 0.16 for fractures of the distal radius compared to hip fracture in women and men.(75)

A high mortality following hip and clinical vertebral fractures is well documented, whereas mortality following other fractures is not as consistently documented.(76) Mortality increases immediately after the fractures and most studies show that the risk mitigate with time.(77-81) In a Norwegian study, hip fracture patients had an increased mortality compared to fracture-free controls with hazard ratio (HR) of 2.3 (95% CI 2.1-2.4).(82) Another Norwegian study on women over 65 years, showed increased mortality three months after a hip fracture, with a HR of 6.5 (95% CI 4.2-9.6).(80) Mortality rates following non-hip fractures are significantly lower than for hip fracture.(75) Other major non-hip-non-vertebral (NHNV) fractures have also been associated with increased mortality about 2 fold for both sexes, though most studies have not shown any excess mortality associated with fractures of the distal forearm.(74, 76, 78, 83, 84) In the Tromsø study, the mortality increased after proximal NHNV fractures, but not distal NHNV fractures.(85) Furthermore, the mortality increased by 89% for women and 77% for men over 50 years of age after any type of subsequent fracture.(85) Up to 30% of the increased mortality after a hip or clinical spine fracture can be attributed to the fracture itself.(7, 79, 86) When examining excess mortality in a Norwegian population-based study, 1 in 10 deaths in women, and 1 in 15 deaths in men were attributed to a fracture.(85) Men have higher mortality following a fracture, and poorer health might be the explanation, but the reasons for the sex-difference is not fully understood.(76, 85) Low BMI, low BMD and low self-perceived health are independently associated with increased mortality.(82, 87-89)

1.6 Treatment of osteoporosis

Management of osteoporosis includes lifestyle recommendation, maintenance of mobility and physical activity, smoking cessation, moderation of alcohol intake, and avoidance of medication with negative impact on the bones if possible. Securing a proper intake of protein, energy, calcium, and vitamin D either through diet or as a supplement is also recommended. Assessment of fall risk and fall prevention is important. However, the Anti Osteoporotic Drugs (AODs) have a much larger fracture preventive effect than lifestyle changes and can be divided into two categories; anti-resorptive drugs and osteo-anabolic drugs.(90)

Recently endocrinologists, and orthopaedic surgeons coordinated and updated the guidelines for medical treatment of osteoporosis in low-energy fracture patients in Norway. This guideline recommends:(91)

- Patients with a hip-, vertebral-, or more than two fractures after the age of 50 years to be treated directly.
- Patients with other types to have DXA scan and/or FRAX calculated:
    - Patients under 65 years should start AODs if T-score $\leq$ -2.5 or FRAX $\geq$ 20%
    - Patients over 65 years should start AODs if T-score $\leq$ -1.5 or FRAX $\geq$ 20%
- Fracture while treated with AODs
    - Consider compliance, change to different type of treatment
    - If $\geq$ 2 fractures consider osteoanabol treatment.

For all patients are recommended vitamin D and calcium supplements. The recommended treatment options are alendronate, zoledronic acid or denosumab.

Women below 60 years of age with osteoporosis can be treated with menopausal hormonal treatment (MHT) after individual assessment of fracture risk, particularly if they have early menopause or menopausal symptoms.(3) However, after the age of 60 years, initiation of MHT solely for fracture prevention is not recommended because of the increased risk of breast cancer and thrombosis.(92)

All these agents have been shown to reduce the risk of vertebral fractures between 50-70% when combined with calcium and vitamin D supplementation. (32) The effect on non-vertebral fracture is in general smaller, and between 15-25%.(32) Treatment with alendronate in postmenopausal women with osteoporosis have been shown to be cost saving in the Scandinavian countries in an economic evaluation from 2007, and later in Norway specifically.(93, 94)

Adherence to treatment is crucial for achieving an effect and reduce risk of fracture. Unfortunately, previous studies have shown low adherence, with one third to half of patients not taking medication as prescribed after 6-24 months.(95, 96) In women over 55 years of age a diagnosis of osteoporosis before any type of fracture or a vertebral- or hip fracture were associated with usages of AODs, however, most women did not receive treatment.(97) A report from European Society for Clinical and Economic aspects of Osteoporosis and International Osteoporosis Foundation (IOF) recommend screening for non-adherence to oral bisphosphonate treatment using bone turnover markers as the amino-terminal propeptide of type 1 procollagen (P1NP) and C-terminal telopeptide of type I collagen (CTX) measured at treatment start and 3 months after.(3, 98)

1.6.1 The treatment gap

Treatment for osteoporosis is readily available and has been shown to reduce the risk of future fractures by 15-70%.(99) Unfortunately the screening for and treatment of osteoporosis is suboptimal and less than 20% of patients that sustain a fragility fracture receives medication to mitigate the future fracture risk.(6) In Norway, only 20% of patients with osteoporosis aged 60-69 years and 35% aged 70-79 years are treated with AOD.(100) The post-fracture treatment gap in Norway is also large; only 16.9% of women and 4.6% of men who suffered a hip fracture is treated with AOD(101) and only 11.2% and 2.7% of women and men, used AOD the first year after a distal forearm fracture.(102)

1.6.2 Fracture Liaison Services

Fracture Liaison Services (FLS) are multi-disciplinary health care models for secondary fracture prevention.(7) The core of an FLS is identification of fragility fracture patients, assessment of osteoporosis and fracture risk, and initiation or recommendation of treatment for osteoporosis and follow-up to ensure adherence. Assessment includes DXA scan for T-score calculation or FRAX-score, examinations for secondary causes of osteoporosis and fall risk evaluation.(103, 104) The aim is to extend the primary care beyond healing of the fracture to also reduce the risk of subsequent fractures.(29) Due to the imminent risk of subsequent fractures, there is a clear benefit in prevention therapy as soon as possible after the first fragility fracture.(5)

The first FLS was introduced in Glasgow, Scotland, in 1999. After the first 8 years of service they evaluated their cost-effectiveness, on a hypothetical population based on the treatments they had provided so far, and the service was cost-effective.(105) In 2012, the Capture the Fracture Campaign were launched by the IOF with the aims to raise awareness to the need for

FLS and set standards for secondary fracture prevention in order to close the care gap in osteoporosis and fragility fracture treatment. Through their Best Practice Framework, they present 13 standards for FLS and an international achievement system where FLSs can be rewarded with either bronze, silver, or gold stars for the quality of their FLS implementation.(103)

Comparison between different FLSs can be difficult, due to different set-ups and outcome measures, but roughly, FLSs falls into four types.(106)

Type A: a service that identifies, investigate, and initiate treatment.

Type B: identify, investigate, and then refers to a general physician for treatment.

Type C: identify patients and informs patient and the general practitioner. No investigations or treatment initiation is performed.

Type D: identify at-risk patients, inform, and educate them, but takes no contact to other health stakeholders in the patient's care.

FLS type A is shown to be associated with increased use of BMD testing, initiation of treatment with AOD, improved adherence to AOD, and lower rates of subsequent fractures.(29, 106-112) However, when no treatment recommendation was made there was no difference in rates of AOD initiation.(29) Furthermore, the less intense models, type C and D, have not shown any reduction of subsequent fracture rates, and lower rates of referrals to DXA scans than type A and B.(29, 106)

The different types of FLS and individual set-ups complicates comparisons and assessment of cost-effectiveness, which is one of the major implementation challenges.(113) The evidence of effect of FLS on subsequent fractures is scarce, and there are few prospective studies and different methodological concerns (different numbers of fractures, services offered, evaluation of subsequent fractures, etc.). Furthermore, there have not been any randomised studies on the effect of FLS prior to the NoFRACT study, to the best of our knowledge.

Some studies have shown a reduction in subsequent fracture rates,(111, 114-119) whereas others have not.(109, 120, 121) The reported reduction in subsequent fracture rates range from 18% to 35%.(111, 116, 117) Furthermore, FLS have a reductive effect on mortality in some studies.(114, 117, 118, 120) Lack of cost-effectiveness studies is also a barrier to clinical implementation of FLS, and larger and long-term studies are needed.(122, 123)

2 Rationale, aim and objectives

Rationale behind the NoFRACT study

When The Norwegian Capture the Fracture Initiative (NoFRACT) was designed in 2014, there were no systematic approach for assessment or treatment of fragility fractures in Norway. Most patients were neither assessed nor treated.(6, 100-102) This treatment gap was the key motivation for the NoFRACT project.

Distal forearm fractures are the most common type of fragility fracture and contribute substantially to the burden of fracture.(17, 24) According to previous studies, Norway, along with the rest of Scandinavia, has the highest incidence of forearms fractures in the world. As forearm fracture is a risk factor for future fractures, including the more severe hip fracture with highly associated mortality.(61, 71, 124) Evaluation and treatment of osteoporosis after a forearm fracture is important to reduce morbidity and mortality.(85) Treatment of osteoporosis is readily available and reduce the risk of future fractures. (99) The increased risk of subsequent fractures and increased mortality after fracture, warrant attention to secondary fracture prevention. FLS is a proposed solution to close the care gap in secondary fracture prevention. However, the lack of large prospective studies on the effect of FLSs on subsequent fracture rates, and mortality is an obstacle for implementation of such interventions. Trials showing firm evidence of effectiveness of FLS is warranted.

The NoFRACT study is a large-scale evaluation of secondary fracture prevention in Norway. The aim was firstly, to improve secondary fracture prevention for patients in Norway by introducing a FLS-intervention, and at the same time evaluate the effect of such an intervention on subsequent fragility fracture rates and mortality. To overcome the ethical challenges of a traditional randomised controlled trial design, we chose a stepped-wedge cluster-randomised trial (SW-CRT) design.

An overview of the size of the challenge is needed for planning of future fracture prevention. Large epidemiological studies on incidence of forearm fractures are limited, and national age- and sex-specific forearm fracture incidence rates and time-trends have not been reported in Norway.(24, 125) This lack of a large epidemiological study on the incidence of forearm fractures in Norway motivated the study presented in Paper III.

The overall aim

The aim of the current project was to design and perform an intervention study to prevent recurrent fractures and describe the burden of forearm fractures.

The specific objectives

Protocol article – Paper I:

Describing the study design, intervention set-up, study outcomes and data analysis planned for Paper II.

The NoFRACT Intervention Study – Paper II:

The objectives were to assess the effect of introducing an FLS standardised intervention program for the treatment of osteoporosis in patients with any type of index fracture on i) subsequent fragility fracture rates (defined as distal forearm fracture, proximal humerus fracture and hip fracture) and ii) all-cause mortality.

The Forearm Fracture Incidence Rates – Paper III:

The objectives were to investigate i) the incidence rates of forearm fractures in Norway among women and men over the age of 20 years from 2008-2019, ii) whether the total and age-specific incidence rates of forearm fractures have changed during the study period, iii) compare mean incidence rate of forearm fractures in summer and winter, and iv) compare in a standardised manner the age-adjusted incidence rates of distal forearm fractures in Norway to previously reported rates of distal forearm fractures in Nordic countries.

3 Materials and methods

3.1 Study design and population

3.1.1 The NoFRACT study - paper I and II

NoFRACT is a multicentre, pragmatic, SW-CRT study, where seven Norwegian hospitals were randomised into three clusters. The SW-CRT design is a relatively new study design commonly used to evaluate intervention in a public health setting for implementation in clinical practice. (126) In the SW-CRT design, each cluster provides data from before and after the intervention. The intervention is introduced to all clusters at different time points, and the order of this introduction is randomized.(126) The SW-CRT design was chosen as it allowed for a randomised trial.(21, 127) The Norwegian Osteoporosis Association randomised the seven hospitals into three clusters and the intervention was introduced with four month intervals between the clusters. The first cluster, included the University Hospital of North Norway, St Olav's University Hospital, and Oslo University Hospital, and was scheduled to start the intervention on May 1, 2015. The second cluster, included Haukeland University Hospital and Molde Hospital, andwas scheduled to start on Sept 1, 2015. The last cluster with Drammen Hospital and Bærum Hospital introduced the intervention on Jan 1, 2016, as scheduled. However, the University Hospital of North Norway was delayed for five months and started on Oct 1, 2015. The seven hospitals were chosen because they represent both small and large hospitals and are spread geographically across Norway (Figure 1). The pragmatic design of this study is outlined in detail in the methods section in the Supplementary (Paper II). In brief, the seven NoFRACT-participating hospitals organised their FLS as preferred locally. The recruitment phase went from May 6, 2015, until Dec 31, 2018, and follow-up throughout Dec 2019. The control phase was from Jan 1, 2011, and until the intervention was introduced at each of the hospitals.

Women and men who were 50 years and older with a low-energy fracture admitted to one of the seven NoFRACT hospitals were eligible for the intervention, either while in the hospital or as outpatients within six weeks after the fracture. Exclusion criteria for the intervention was high-energy fractures or fractures of fingers, toes, skull, or face. Furthermore, very fragile patients with short life expectancy were not offered the intervention. Therefore, patients ≥100 years were excluded from the analysis, as they were not likely to have received the intervention. A total of 100,198 women and men were included in the analysis: 57,186 patients in the control group, 47,071patients in the intervention group, and 4,059 patients were in both groups. Due to

the definition of index fracture (first fracture of any type after a fracture-free period of 3 years) fracture patients could be included in both the control group and the intervention group.

Figure 1: Map of the NoFRACT hospitals.

3.1.2 The Forearm Fracture Incidence Rates – Paper III

An observational retrospective epidemiological register study using data from the NPR was designed to investigate the incidence rates of forearm fractures in women and men aged above 20 years in Norway from Jan 1, 2008, to Dec 31, 2019.

We included all women and men over the age of 20 years treated as in- and outpatients for a forearm fracture between Jan 1, 2008, and Dec 31, 2019. We included a total of 181,784 forearm fractures during 12 years and 45,628,418 PY.

3.2 The NoFRACT FLS-Intervention – Paper I and II

The intervention was a FLS model of care for secondary fracture prevention that consisted of a systematic identification, assessment, and treatment of osteoporosis. A study nurse identified patients based on hospital records with International Classification of Diseases 10th Revision (ICD-10) codes. A nurse contacted the patients, either in person while in hospital or by letter

after discharge and invited them to the FLS. Blood samples were collected for measurement of serum levels of 25-hydroxyvitamin D, calcium, parathyroid hormone, thyroid-stimulating hormone, albumin, and creatinine to eliminate secondary causes of osteoporosis and to assess the kidney function.

BMD was measured at the hip and lumbar spine with DXA and/or the FRAX 10-year probability for MOF and hip fracture was calculated. The nurse provided lifestyle advice that are important for bone health such as maintaining physical activity, moderate alcohol consumption and quite smoking. All patients were recommended a healthy diet and sufficient intake of calcium and vitamin D through diet or as supplementation, of 500-1000 mg calcium and 800 IU vitamin D daily. If necessary, the patients were referred to fall prevention programs.

A physician wrote a report with a summary of the results from the measurements and assessment of future fracture risk in the medical record and recommended treatment based on type of fracture, comorbidities, in accordance with the study protocol, and prescribed AOD to:

i) Patients with a hip fracture, a vertebral fracture, or two or more low-energy fractures directly, without any need of BMD or FRAX score assessment,

ii) Patients with their first low-energy fracture and BMD T-score ≤ -1.5 or FRAX score for MOF >20%.

Information on the results of the individual assessments and the prescribed AOD was sent to both the patient and to their primary care physician.

Treatment options in the FLS

Intravenous zoledronic acid was the primary drug of choice for patients with a hip fracture, preferably administered during the hospitalisation. For patients with their first low-energy fracture, other than hip or vertebral fractures, oral bisphosphonate was the drug of choice, otherwise denosumab was recommended in case of reduced kidney function (estimated Glomerular Filtration Rate 20-35 mL/min). Patients with BMD T-score ≤ -3.5, or subsequent low-energy fracture while on anti-resorptive treatment, were referred to an osteoporosis-specialist to consider osteoanabolic treatment. AOD was initiated while the patients were hospitalised or recommended initiated within six weeks of the index fracture.

For follow-up, the patients who had AOD treatment prescribed, were contacted by the coordinating nurse three months after the prescription by phone, to clear out misunderstanding

and take care of potential adverse effects of the treatment. Another phone consultation was offered after 12 months. These phone consultations were conducted to improve adherence.

3.3 Outcomes and other variables

3.3.1 The NoFRACT study - paper II

The primary outcome of the SW-CRT was change in the rate of subsequent fragility fracture (distal forearm, proximal humerus, and hip) after any type of index fracture. The secondary outcome was all-cause mortality. Additional outcomes were the change in rate of any type of subsequent fracture (except finger, toes, face, and scull), and subsequent hip fracture after any type of index fractures, and a second hip fracture and mortality after an index hip fracture.

We used data from national registers for the analysis,

NPR provided data on fracture type, fracture date, sex, birth year, hospital, hospitalisation dates, municipality of residence, surgical procedure codes, and Charlson Comorbidity Index, which was based on other diagnosis from the same year as the index fracture. Both the number and the severity of diseases, according to the estimated 1-year mortality hazard ratio, was summarized into a weighted index between 0 and 15 (no – maximum comorbidity) for this index.(128) Statistics Norway provided data on dates of migration and death, marital status, country of birth. As well as the urban centrality index for each municipality as a score from 1 – 6 (most – least central) based on the number of inhabitants and driving time from residential housing to jobs and services,(129) and the educational level (<12 years, 12 years and >12 years).

All Norwegian citizens have a personal identification number. NPR replaced the personal identification number with a study id, and this was for merging of the data from the different registers. We received de-identified patient-level data from the NPR on all patients with fractures treated at all Norwegian hospitals, both as in- and out-patients.

3.3.2 The Forearm Fracture Incidence Rates – Paper III

Primary outcome was overall numbers and age-standardised incidence rates of forearm fractures between 2008 and 2019 in Norway among women and men over 20 years of age. Additional outcomes were i) overall numbers and age-specific incidence rates of distal and proximal forearm fractures, ii) comparison of mean incidence rate of forearm fractures in summer- and wintertime, and iii) comparison of standardised incidence rates of distal

forearm fracture in Norway to standardised incidence rates from previous studies from other Nordic countries (Denmark, Finland, and Sweden).

We used de-identified patient-level data from the NPR on all patients with forearm fractures treated in Norwegian hospitals and large emergency units/departments between Jan 1, 2008, and Dec 31, 2019. Statistics Norway provided data on background population demographics on Jan 1, of the years 2008-2020.

3.4 Definition and classification of types of fracture

3.4.1 The NoFRACT study – Paper I and II

Any type of index fracture or subsequent fracture was defined as fractures with the following ICD-10 codes: S22 (rib, sternum, and thoracic spine), S32 (lumbar spine, pelvis), S42 (shoulder, upper arm), S52 (forearm), S62 (wrist, hand except fingers S62.5-7), S72 (femur), S82 (patella, lower leg, and ankle), and S92 (foot except toes S92.4-5).

Subsequent fragility fractures were defined as fractures with ICD-10 codes S52.5-S52.6 (distal forearm), S42.2 (proximal humerus) and S72.0-S72.2 (hip).

Index and subsequent hip fractures were identified based on the ICD-10 discharge codes S72.0-S72.2 and Nordic Medico-Statistical Committee (NOMESCO) surgical procedure codes (NCSP). A three-week washout period was applied, and we used the same procedure for quality assurance as the Norwegian Epidemiologic Osteoporosis (NOREPOS) Study hip fracture database.(130)

For identification of incident fractures from the NPR we combined ICD-10 discharge codes and NOMESCO surgical procedure codes. We excluded patients with a code for fracture control or follow-up treatment (ICD-10 Z-/T-codes), and/or a NCSP code for reoperation.

Classifications of fractures other than hip fractures:

Based upon NCSP codes, we grouped the fractures as:

i) "Certain acute" if there were an NCSP code for treatment with a plastering, reposition, acute prosthetic treatment AND no control visit code.

ii) "Possibly acute" if it was the first fracture registration AND there was no control visit- or reoperations code AND it was not coded as "Certain acute".

iii) "Certain follow-up visit" if this was not the first registration AND there was a control visit- or reoperation code.

iv) "Possibly follow-up visit" if it was the first registration AND there was a control visit code; OR if it was the first registration and there was a reoperation code; OR if it was not the first registration AND there was no control visit- or reoperation code AND it was not code as "Certain acute".

We performed a wash-out of 30 days between registrations categorised as "Certain acute" or "Possibly acute". "Certain Controls" were excluded from the analyses. We performed a wash-out of six months between registrations categorised as "Possibly Control".

This was done within each ICD-10 group of fractures. Furthermore, we applied a 30-day wash-out period for fractures within the same region of the body, ex. The arm: S42, S52 and S62, as fractures can be miscoded. Lastly, we applied a six-month wash-out period between fractures within the same ICD-10 group.

Data on fractures from 2008-2010 were excluded due to inconsistent coding with lack of hospital specific data from two study sites (The University Hospital of North Norway and Oslo University Hospital) in this period. This was necessary due to the cluster design and the analysis of data in the NoFRACT intervention study. However, information about fractures during 2008-2010 was used to define consecutive fracture number during the study period.

3.4.2 The Forearm Fracture Incidence Rates – Paper III

Identification of forearm fractures was performed in the same manner as in Paper II. We defined ICD-10 code S52.0-S52.1 as proximal forearm fractures, S52.2, S52.3 and S52.4 as forearm shaft fractures, S52.5 and S52.6 as distal forearm fractures, and S52.7, S52.8 and S52.9 as other forearm fractures. The ICD-10 code S52 with subgroups (main or additional diagnosis) was combined with NCSP codes. Patients with a fracture follow-up code (ICD-10 Z-/T-codes), and/or a NCSP code for reoperation were excluded from the analysis, except for patients where the first fracture registration was a follow-up code. This was chosen as an attempt to include patients who not were initially treated in the secondary health care but captured at follow-up.

For patients with more than one fracture we set a washout period of 6 months between two fractures. Finally, we set a maximum of two fractures per person in the study period to avoid including and misclassifying prevalent fractures as incident fractures.

3.5 Statistical analyses

Categorical variables were presented as numbers with percentages (%) and continuous variables as mean ± standard deviations (SD). All statistical analysis was performed in STATA (version 16, StataCorp LP, TX, USA).

3.5.1 The NoFRACT Intervention Study – Paper I

In Paper I, the sample size calculation for the NoFRACT study was performed. Assuming inclusion of 82,467 patients with any type of fracture and 80% power, the study could detect a relative risk of 0.73 of subsequent fracture in the intervention group versus control group, (intra-cluster correlation =0.03, cluster size=357). Sample size calculations were based on previous studies,(70, 109, 114, 115) and calculated using the "steppedwedge" command in STATA (version 15 (StataCorp LP, TX, USA).

3.5.2 The NoFRACT Intervention Study – Paper II

For the analyses, data from all patients >50 years of age who were treated for any type of an index fracture at a NoFRACT hospital were included, regardless of exposure to the intervention. Analyses were performed according to the intention-to-treat principle. In the register data that we used for the analyses, we had no information on whether the patients with fractures had received the FLS-intervention, had AOD prescribed, or were adherent to AOD.

Time of the index fracture defined if a patient was included in the control group or intervention group. Patients with index fractures during the intervention period (years 2015-2018), were compared to the control group of patients admitted before the intervention (years 2011-2015). Each hospital acted as its own control. We defined an index fracture as the first fracture after a fracture-free period of 3 years (washout 2008-2010). Therefore, patients in the control period could appear more than once in the control period as well as in both the control period and the intervention period if there were more than 3 years between the fractures. A multilevel model was used to handle repeated outcomes by individual.

Follow-up time was calculated for each person as the time between an index fracture and the first subsequent fracture, death, emigration, or end of follow-up Dec 31, 2019. Total numbers of index and subsequent fractures were calculated. Kaplan-Meier curves were constructed based on the intervention status.

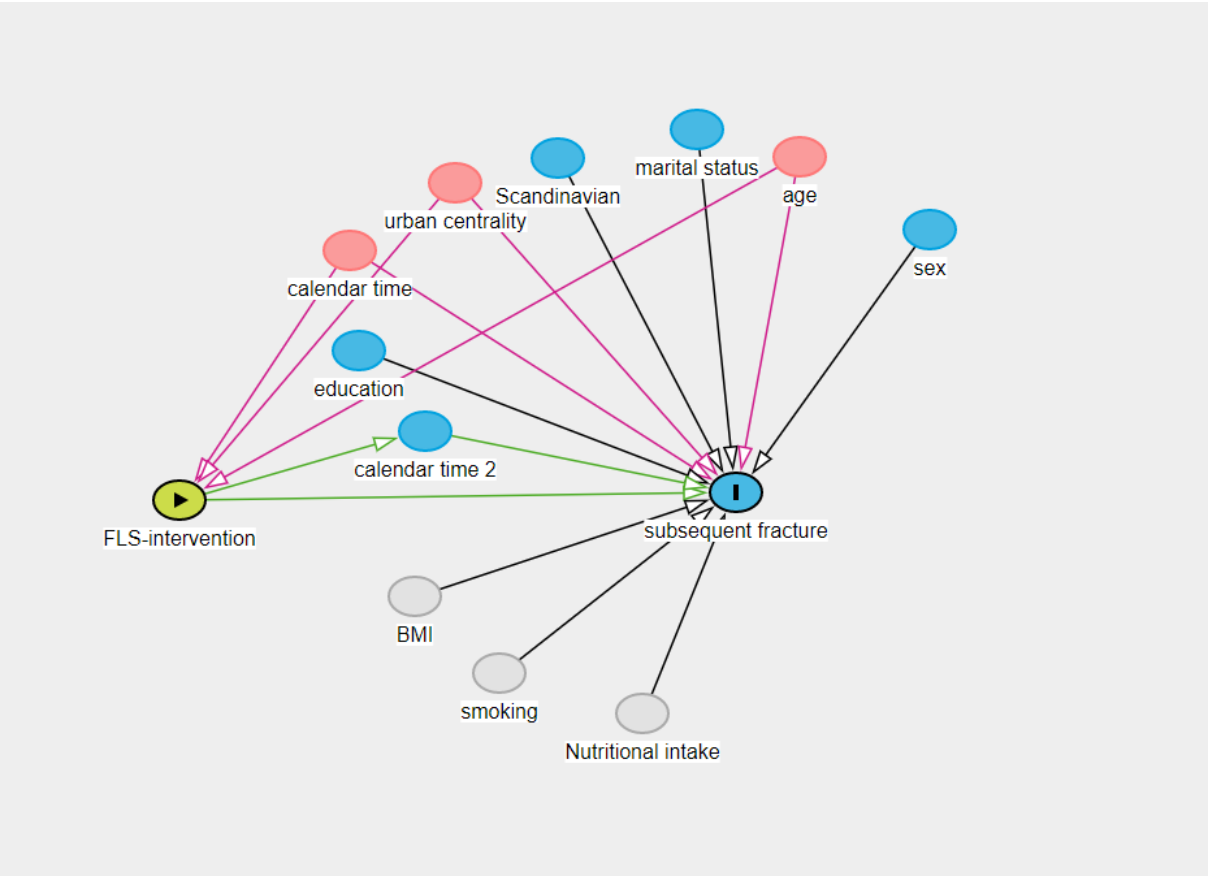
Cox regression analysis was used to calculate hazard ratios (HRs) with 95% confidence intervals (CI) for primary and secondary analyses of time elapsed: i) from any type of index fracture to a subsequent fragility fracture, ii) from any type of fracture to death. For additional

analyses; iii) from any type of index fracture to any type of subsequent fracture, iv) from any type of index fracture to a subsequent hip fracture, v) from an index hip fracture to a second hip fracture, vi) from an index hip fracture to death.

Proportionality of the HRs were verified using log-log plot of survival by intervention status, adjusting for age, sex, hospital, time. When we estimated HR, tand he first model was adjusted for; i) age, sex, clustering by person, stratified on hospital, and whether the fracture was the first, second or third fracture etc., ii) the second model was additionally adjusted for marital status, educational level, urban centrality index,(129) Scandinavian-born, fracture type, and comorbidity, iii) the third model was additionally adjusted for hospitalization day (in splines with 7 knots).

We used stratified Cox proportional hazard models to account for the difference in risk of subsequent fracture by hospital and allowed hospitals to act as their own control with individual baseline functions. Clustering by individual was taken into account, because fracture patients could be included in both the control period and the intervention period, due to the definition of the index fractures. Whether the fracture was the first, second or third fracture etc. was taken into account, because the fracture risk increases by number of fractures. Due to the design of the study, more patients in the intervention group had previous fractures compare to the control group. Because subsequent fracture rates for hip fracture have declined the last 20 years(127) and the randomisation in the SW-CRT design are time-dependent, the analyses were adjusted for time in the form of day of hospital admission/outpatient consultation of the index fracture (cubic spline with 7 knots) to account for time trends. The potential confounders were selected using a causal directed acyclic graph (DAG) as shown in Figure 2.(131)

Figure 2: Directed acyclic graph for the NoFRACT project



Sensitivity analyses

We performed five sensitivity analyses: i) including a transition window, excluding fractures occurring ± 4 weeks of the randomisation time. This analysis was performed to allow for the intervention to settle in, but also to allow for study sites to have been too eager to introduce the intervention. ii) excluding patients with home-address outside the catchment area of the hospital (N=17,937), iii) excluding index fractures in the intervention period from patients with previous fractures from the control period, iv) including time as running month instead of day for hospitalisation, and v) adjusting for fracture number including all fractures occurring from 2008 to 2018.

3.5.3 The Forearm Fracture Incidence Rates - Paper III

We calculated midyear populations based on data on population demographics from Statistics Norway from Jan 1, 2008 - Dec 31, 2020. Mid-year populations were calculated as the mean of the population with the age X of the respective year, and the population with the age X+1 the

following year. Age- and sex-specific incidence rates of forearm fractures per 100,000 PY was calculated using mid-year populations in 1-year age groups.

Age-standardisation of forearm fractures was performed by the direct method, and separately for women and men, using the mean of the age distribution in Norway in 1-year age groups as standard population. Time-trends were investigated; using linear regression to evaluate change in the total number of fractures per year and change in age at first fracture over time (retrieving β with 95% CI), and negative binomial regression (Incidence Rate Ratios with 95% CI) to evaluate change in age-adjusted incidence rates over time.

Patients experiencing fractures in the period 2008-2010 were excluded from the calculations of mean age at first fracture, as an attempt to exclude those with multiple forearm fractures in calculation of mean age at first fracture. Mean incidence rates of forearm fractures in women and men in summer- and winter-time were compared. We defined summer as June – August, and winter as December – February.

When we compared incidence rates of distal forearm fractures between Nordic countries, we performed a standardised comparison of age-adjusted incidence rates of forearm fractures because a direct comparison of incidence rates is challenged by differences in demographic compositions with regards to proportions of women and men in different age groups. We obtained number of distal forearm fractures and PY from previous Nordic (Denmark, Finland, and Sweden) studies, where this information was available and comparable with our data. By direct method using the mean age distribution of all included studies as the reference we calculated standardised incidence rates. These incidence rates were compared by negative binomial regression.

Sensitivity analyses

In Paper III, the analyses were based on data from secondary care, but included first-registration fractures even if they had a follow-up code. Dahl et al. reported that 7% of forearm fractures in Norway are treated only in primary care, however, they concluded that this may be an overestimate because diagnosis were based on tentative diagnosis that could not be confirmed as certain forearm fractures.(132) To examine whether the time trends changed when including fractures from primary care, we performed three sensitivity analyses using data from the Dahl et al. study;(132) i) without fractures treated only in primary care or coded as follow-up, ii) without fractures treated only in primary care, but with first fracture registrations coded as

follow-up, and iii) including fractures treated only in primary care and first fracture registrations coded as follow-up.

3.6 Ethics

The NoFRACT intervention study and the study of incidence rates of forearm fractures have received approval from the Regional Committees for Medical and Health Research Ethics, Region South-Eastern Norway, for the merging of data from national registers and exemption from obtaining consent from the patients with fractures (REK 2015/334). All data was de-identified, and the decryption code was retained by the NPR. Data was kept at a research platform for sensitive data at the University of Oslo that ensures data security is sufficient and in accordance with the General Data Protection Regulation.

4 Main results

4.1 The NoFRACT study – Paper II

A total of 100,198 women and men suffered an index fracture of any type between Jan 1, 2011, and Dec 31, 2018. The mean age at fracture was 69.9 years (range 50-99) and 66% were women.

In total, 8,998 (9%) patients experienced a subsequent fragility fracture (distal forearm, proximal humerus, hip) after any type of index fracture during a median follow-up of 3.1 years. The FLS was associated with a reduction in risk of a subsequent fragility fracture of 12% when both sexes were analysed combined (HR 0.88, 95% CI 0.84-0.92), by 12% in women (HR 0.88, 95% CI 0.84-0.92) and 10% in men (HR 0.90, 95% CI 0.82-0.99). In total, 20,198 (20%) patients died during follow-up of maximum 4.7 years. The FLS reduced mortality after the first index fracture of any type by 26% (HR 0.74, 95% CI, 0.72-0.77).

The FLS was associated with 5% lower risk of any type of subsequent fracture (HR 0.95, 95% CI 0.92-0.99) and 24% lower risk of subsequent hip fracture (HR 0.76, 95% CI 0.71-0.81) after any type of index fracture, and 22% lower risk of a second hip fracture after an index hip fracture (HR 0.78, 95% CI 0.70-0.88). All the sensitivity analyses showed similar results.

4.2 The forearm fracture incidence rates – paper III

We identified 181,784 forearm fractures in 45,628,418 PY in women and men above 20 years of age between 2008 and 2019. The mean annual number of fractures was 15,148 (95% CI 14,575 -15,722), and it increased during the study period. The mean annual incidence rate of forearm fractures was 565 (95% CI 550-580) per 100,000 PY in women and 231 (95% CI 228-234) per 100,000 PY in men. The age-adjusted incidence rate of forearm fractures declined for men by 3.5%, but was stable for women from 2008 to 2019.

The mean number of distal- and proximal forearm fractures was 10,492 (95% CI 10,112 – 10,872) and 2,290 (95% CI 2,159 – 2,422). The mean annual incidence rate of distal forearm fractures was 747 (95% CI 724-769) in women and 178 (95% CI 174-183) per 100,000 PY and men over 50 years. The age-adjusted incidence rates of distal forearm fractures declined by 4.7% in women and 7.0% in men. The mean annual incidence rate of proximal forearm fracture was 70 (95% CI 66-72) in women and 51 (95% CI 50-53) per 100,000 PY in men.

In women over 20 years, the mean annual incidence rate of forearm fracture per 100,000 PY was significantly higher in winter (1142; 95% CI 1,068-1,215) compared to summer (802; 95%

CI 752-853), p < 0.001, but not in men (462; 95% CI 361-562 vs. 362; 95% CI 291-434), p=0.11.

When compared to Finnish (133) and Swedish (24) studies, incidence rates of distal forearm fractures in Norway were not significantly different among subjects 20 years and older. However, compared to a Danish study, incidence rates of distal forearm fractures in Norway were lower in women (p<0.001), but not in men (p=0.072).(125)

Sensitivity analyses

The sensitivity analysis showed similar results without forearm fractures treated only in primary care or coded as follow-up in the first registration. However, when including forearm fractures treated only in primary care and first fracture registrations coded as follow-up the overall incidence of forearm fractures per 100,000 PY increased from 565 (550-580) to 586 (570-603) in women and from 231 (228-234) to 251 (247-255) in men, approximately 6%. However, inclusion of these fractures did not change the time-trends for age-adjusted incidence of all forearm fractures from 2008-2019.

5 Methodological considerations

5.1 Internal validity

The validity refers to how well the results in a study represent true findings in individuals outside the studied population. Systematic errors are threats to internal validity. The three major types of systematic errors are selection bias, information bias, and confounding.

Analyses in both the NoFRACT intervention study and incidence rates of forearm fractures are based on data from the NPR. Methodological considerations in relation to NPR will be discussed together.

5.1.1 Norwegian Patient Registry

The NPR is not a research register, but a register with the purpose of management, administration, financing and quality assurance of specialist care. NPR was established in 1997, and from 2008 and onwards it has held individual level data on patients treated in all public specialist health-care services in Norway.(134)

Selection bias

Norway has a single-payer health care system founded on the principles of universal access. We would therefore expect most of the fractures treated in secondary health care to be registered in the NPR. However, some patients with fractures treated solely in primary sector or treated abroad may not have been counted in the study. We did include fractures with an ICD-10 code for follow-up visits if it was a first-time registration. Inclusion of these patients was an attempt to include those treated in primary care and thereby reduce selection bias. Because fractures initially treated in primary care before being referred to hospital, are sometimes coded as a follow-up visit and not as an incident fracture. We did not include data from primary care as they are less specific and because little is known about the validity of data on fractures treated only in primary care. Furthermore, we performed a sensitivity analysis including data on patients with forearm fractures treated only in primary care in Paper III, to test if time-trends changed, and this was not the case.

Information bias

Information bias can occur if there is error in the either information from participants or measurement. The use of register data is highly dependent on the validity of the registers, the validity can be evaluated on sensitivity (completeness) and PPV (accuracy) of the measured variables.(135)

Because of the single-payer health care system in Norway we expect registers to have high completeness. However, because the NPR is made for reimbursement this may influence the accuracy of medical coding, especially with respect to coding of main versus additional codes for increased reimbursement.(135) It is well described that the prevalence of additional codes has increased over time, perhaps as a result of the reimbursement systems. All Norwegians have a personal identification number and by using this number we were able to link data from different registries. The reporting of personal identification numbers to the NPR was nearly complete (99.4%) in 2017, but this has improved over time since 2008.(134) Because of this, the first years of the study of forearm fracture incidence rates might have underreporting of S52 diagnosis due to lack of personal identification numbers in the NPR. We therefore performed an analysis only including data from 2011-2019, and the number of fractures still increased significantly over time, 257 fractures per year, p=0.01. For comparison the number of fractures significantly increased with 211 fractures per year from 2008-2019.

Data in NPR is quality checked by National Services for Validation and Completeness Analyses on different major health care diagnosis. Here data for NPR is compared to medical quality registries. This has been performed for the hip fracture diagnosis, and completeness of NPR was 88.4% from 2008-2012 and 96.7% from 2013-2014.(136) The increase in completeness over time could have affected the results in the NoFRACT intervention study in Paper II, as data from the earliest years may have lower completeness than from the later years of the study, resulting in an underestimation of the effect in the study. However, analyses of completeness in NPR have not been performed for other types of fractures. Furthermore, the registration of the hip fracture diagnosis is likely to be better than for other types of fractures, as hip fractures are almost always treated surgically. When analyses of data in Paper II was performed, the accuracy of the fractures registered in NPR had only been investigated for hip fractures, and was found to be 93.5% in 2011–2012.(137) The accuracy of identification of hip fractures in NPR has been evaluated on data from 2008-2009.(138) Here a combination of ICD-10 and NOMESCO codes for identification of hip fractures in NPR had an accuracy of 99.4% (95% CI 96.5-99.9%). These finding were in accordance with the almost complete coverage of the hip fracture diagnosis in NPR shown in the NOREPOS study.(139) The syntax used to define hip fractures in Paper II was the same as the one used in the NOREPOS study. We also combined ICD-10 diagnosis codes with NOMESCO procedural codes for identification of fractures, to minimize the risk of misclassifying prevalent fractures as incident fractures and thereby increase the accuracy. However, the use of ICD-10 codes made it impossible to

distinguish between left/right side fractures and bilateral fractures are counted as only one fracture.

The use of a wash-out period may have contributed to both over- and under-registration of fractures, as some patients might have fractured more than once within six months and other may have had control visits that were miscoded more than six months after the fracture.
In Paper III, the use a six-month washout period may have left out some incident forearm fractures. In an Icelandic study on 2364 medical records verified incident forearm fractures, 2% of patients with a first forearm fracture sustained a second forearm fracture within six months (61). This probably has affected the sensitivity of our results somewhat. We also validated the forearm fracture diagnosis in women and men over 19 years who were treated at five hospitals in 2015.(140) From radiological departments, a total of 7256 x-ray reports from 5440 patients were retrieved and reviewed. In that same study, we tested three-, six-, and 12-months washout periods, and with a six months wash-out period the sensitivity was 90% and the PPV increased from 74% to 90%. When we combined a six-month wash-out period with follow-up codes, and procedure codes the PPV increased, but the sensitivity decreased from 90% to 69%. (140) Still, we cannot rule out that some fractures might have been miscoded and thereby result in information bias. With the limitation of maximum 2 fractures per person, we excluded 998 (0.5%) of the fracture registrations. A fracture register study from Sweden indicated that 0.2% of patients had a new distal radius fracture in the same wrist within three years, indicating that we were right to only include two fractures per person. However, the finding also tells us that we are likely to have excluded some patients with recurrent wrist fractures in the same wrist.(30)

5.1.2 The NoFRACT study - paper I and II

Selection bias

The use of register data ensured the size of the study, prevented loss to follow-up, limited selection biases, and ensured that the same method was used to identify fractures at all hospitals during both the control period and intervention period. Furthermore, follow-up time from index fracture to a subsequent fracture, death or end of follow-up was calculated similarly for all patients.

The analyses were based upon data from registers, with inclusion of all patients with a fracture who were treated at one of the NoFRACT hospitals, regardless of receiving the intervention or not. Given the standardised protocol for screening of fracture risk at the different study sites

and the inclusion of all patients seeking hospital for treatment of fractures in the analysis, there is probably less selection bias in this study compared to previous studies. However, the consequence of this intention-to-treat design is that the effect of the intervention might have been diluted. From collection of quality assessment data at each NoFRACT hospital, about 78% of patients with a fracture was invited to the FLS-intervention, 70% had assessment of osteoporosis or their fracture risk assessed in the intervention period, and 56% had AODs prescribed. In the register data that we used for the analyses, we had no information on whether the patients with fractures had received the FLS-intervention, had AOD prescribed, or were adherent to AOD.

Despite of the intention-to-treat design, we may have a small selection bias in the intervention, due to our protocol. The very fragile patients, those with short lifetime expectancy were spared from the intervention and some patients refrained from receiving the FLS-intervention. In previous Norwegian studies non-participants had poorer health status, had higher mortality, higher prevalence of chronic disease and lower socioeconomic status.(141, 142) Thereby, the potential effect of FLS on mortality could be underestimated, by not exposing those who are most likely to benefit from the intervention. Furthermore, we had no information on trauma mechanisms in the register data and could therefore not distinguish between high- or low-energy fractures in the analyses. For the FLS intervention, we only invited patients with low-energy fractures. However, in a large cohort of over 60,000 women and men from Canada, patients with high-energy fractures showed similar associations between low BMD and increased risk of subsequent MOF as those with low-energy fractures.(143) This might have reduced the effect of the intervention as these patients were most likely included in the analyses. Whether or not this group of patients should be offered FLS or not needs to be investigated in further studies including whether the advantages of offering the intervention to this group is larger than the disadvantages on a societal level.

Lastly, we might have selection bias in the sample of hospitals included in the study. The personnel at all these hospitals were eager to participate in the study and may therefore already have been aware of osteoporosis in fracture patients. This could mean that the effect of introducing an FLS intervention may have been smaller than in other hospitals because the intervention started earlier than planned (if the hospitals already were good at capturing and treating patients with high subsequent fracture risk). On the other hand, it could also mean that the personnel were more motivated than personnel at other hospitals

and that the effect of the intervention would be smaller if introduced at all hospitals in Norway.

Confounding

Confounding is a phenomenon where the association between two variables is explained by a third variable – the confounding variable. To be a confounding variable, the variable must be associated with both the exposure and the outcome variable. For potential confounders, we drew a causal DAG,(131) Figure 2. Based on the DAG, analyses were adjusted for age, sex, marital status, educational level, urban centrality index(129), Scandinavian-born (Denmark, Norway or Sweden), Charlson Comorbidity Index(128) fracture number and type of index-fracture. However, by using pre-existing register data for outcomes measures, the selection of outcome variables and information on potential confounders were limited. For example, we had no information on BMI, smoking, or nutritional intake. Adjustment for BMI could have affected the results as low BMI increase the risk of fracture, whereas a high BMI, up to a certain point, reduce the risk of fracture.(48) Mean BMI have increased in Norway over the time of the study.(144) This could have had an impact on the risk of fracture. Daily smoking has reduced in Norway from 5.9% to 1.5% from 2010 to 2018.(145) However, the usage of snuff have increase in the same years, and approximately 20% used snuff daily in 2018. However, this is especially pronounced in younger people under 35 years.(145) Smoking increases the risk of osteoporosis and fracture, (54, 55) so a reduction in smoking over the time of the study could lead to a lower risk of fracture. Evidence on snuff and osteoporosis in adults is scarce, however a relationship between any type of tobacco and loss of bone mass in the oral cavity in humans are reported.(146) We did adjust for education, which can be used as an instrument variable in register based studies as it is strongly associated with life style factors such as diet, physical activity and smoking.(135) Such data on education often have higher validity than self-reported data on life-style factors.

Furthermore, analyses were stratified on hospital to allow for differences in risk of subsequent fractures between hospitals. This was done because the hospitals in the NoFRACT study represents both small and large university hospitals, and they are located all over Norway, Figure1. There have not been made studies on the risk of subsequent fracture rates comparing urban to rural areas. However, previous studies have shown higher rates of forearm and wrist fractures in urban areas compared to rural.(8, 56) Clustering by individuals were taken into account, because patients could be in both the control and the intervention period. Individuals could appear in both groups because the same inclusion criteria (fracture of any type except

fractures in finger, toes, face, and skull after a fracture-free period of 3 years) were used for all participant at all times in the study. This was done to make sure that inclusion criteria were similar in the control group and intervention group. However, these adjustments did not change the main results.

The randomisation in an SW-CRT is time-dependent. Time is therefore an important confounder in SW-CRT designs with longer follow up and must be adjusted for to avoid misinterpreting reduction in fracture rates by time as an effect of FLS.(147). Previous studies have showed declining subsequent hip fracture rates during the last 20 years(127) and declining incidence of distal forearm fractures in Norway. (14, 23) We therefore adjusted the analyses for time in the form of day of hospital admission/outpatient consultation of the index fracture and this did not change the results. Additionally, we performed a sensitivity analysis adjusting for time in form of month of hospital admission/outpatient consultation, and this did not change the results. This support the evidence that the lower risk of subsequent fracture and mortality in the intervention group is associated with the FLS, and not due to time-trends in fracture rates.

Study design

The choice of a SW-CRT design is challenging, as the design works best with an intervention with an immediate effect on outcomes. The delayed effect of the intervention may lead to loss of power, if it is not possible to test the effect within the timespan where some clusters are still in the control period.(148) This was unfortunately not possible for our study due to practical reasons and the intervention was rolled out over eight months, with four months intervals between three clusters The effect of oral bisphosphonates on fracture risk of NHNV fractures, is evident after more than one year of treatment, whereas the effect of zoledronic acid and denosumab is evident after six months.(149) Thereby, the effect of AODs is not effective within the timespan of each cluster which may affect the power of the trial. Furthermore, introduction of the intervention was five months delayed in Tromsø, and we adjusted for this in the analysis, but the delay can have affected the power of the study.

5.1.3 The Forearm Fracture Incidence Rates - Paper III

Selection bias

As this nationwide study was based on register data from all hospitals in Norway, selection bias was assumed to be limited.

Information bias

Information bias are described under 5.1.1 Norwegian Patient Registry

Confounding

In Paper III, we did not explore any causality or associations between an exposure and forearm fracture; thus, confounders are not an issue in this study.

5.2 External validity

The external validity of a study is the extent to which the results of the study transfer to a generalised population.

The magnitude of the NoFRACT study cohort included in Paper II and the wide inclusion criteria secured the generalisability of the study to the Norwegian population over 50 years with a fracture. As the study cohort included in Paper III was based on the entire population, it is representative of the Norwegian population over 20 years with forearm fractures.

6 Discussion of main findings

The following section will discuss the results of the studies included in the thesis in a broader perspective.

6.1 Protocol article – paper I

The protocol article presents the study design, treatment algorithm in the FLS and a statistical plan for the analyses.

In the NoFRACT study we included patients with any type of index fracture, except for fingers, toes and skull, over the age of 50 years at the time of fracture. These patients may have a lower risk of subsequent fragility fractures compared to patients in the other studies. Previous studies that showed effect of an FLS intervention inclusions criteria have included patients over 50 years of age with non-vertebral fractures(117) or MOF(116); or patients over 60 years of age with a hip fracture.(120)

The treatment algorithm in the NoFRACT study recommended treatment to patients with a hip/vertebral fracture or two or more low-energy fractures without any need of BMD or FRAX score assessment and for patients with their first low-energy fracture if BMD T-score ≤ -1.5 or FRAX score for MOF >20%. The recommendation of treatment at a BMD T-score of ≤ -1.5 is more liberal than the guideline from the orthopaedic and endocrine association in Norway for treatment of osteoporosis in Fracture Norway. In that guideline, this is only recommended in patients $\geq$ 65 years, and for patients under 65 years BMD has to be below -2.5.(91) A concern with the wide inclusion criteria and secondary screening for osteoporosis in fragility fracture patients is over diagnosis and treatment of osteoporosis. However, a previous Norwegian study have shown under-treatment of patients with high risk of fracture, defined as FRAX $\geq$ 20% for MOF or BMD T-score $\leq$ -2.5.(150) This was evaluated based on FRAX without BMD in 28,461 women and men aged 50-85 years. In a subgroup of 6,860 women and men BMD was measured and only 24% of women and 16% of men with a T-score less than -2.5 were treated with AODs. The under-treatment of patients with high risk of osteoporosis was stable from 2006 to 2016.(150) The age group in this study corresponds well with those assessed for osteoporosis in the NoFRACT study, and suggests that measures for prevention of fragility fractures in Norway is needed. Under-treatment is obviously a larger problem than over-treatment.

The protocol article also presents the statistical plan for the analyses. However, we had to make some changes to this plan. In the protocol article we wrote that missing data would be dealt

with by multiple imputation, the use of register data with less than < 1% missing data in some variable made this redundant. More importantly we changed the statistical model for analysing the data; we planned use a generalised linear mixed models for binary outcome data (fracture/no fracture) and include clustering by hospital by including hospital as random effects. However, after consulting several statisticians we ended up using a stratified Cox model this allowed hospitals to act as their own control with individual risk of subsequent fracture by hospital.

6.2 The NoFRACT study - paper II

The overall findings of Paper II were that the FLS introduced in NoFRACT reduced the risk of subsequent fragility fractures, fracture of any type, hip fracture, and mortality after a first index fracture of any type, and the risk of a second hip fracture after an index hip fracture.

In previous studies, the reduction of subsequent fracture risk ranged from 18% to 35%, (111, 114-119) while some studies reported no change.(109, 120, 121) However, due to the difference in design of the previous studies, comparisons should be done carefully.

After implementation of a minimal resource FLS in Sweden in 2013, Axelsson et al. showed a 51% reduction in x-ray verified re-fractures in patients treated for osteoporosis compared to untreated patients.(109) However, when comparing recurrent fractures rates before and after the implementation they found no significant difference (8.3% vs. 8.4%, p=0.85).(109) In 2020, Axelsson et al. reported an 18% reduction in recurrent fracture rates at two hospitals implementing an FLS, while no change in recurrent fracture rates at two hospitals without FLS.(116) During the same period, from 2012-2017, there were no evidence of change in temporal trends in the rate of recurrent fractures.(116) In the Netherlands, implementation of guidelines for osteoporosis assessment and fall prevention for patients over 50 years with a non-vertebral fracture reduced the risk of a subsequent fracture by 35%, and mortality by 33%.(117) In that study, the control group were enrolled from 1999-2001 and the intervention group from 2004-2006.(117) A study from 11 hospitals in the UK evaluated the effect of an orthogeriatric- and nurse-led FLS on post-hip fracture mortality in patients 60 years or older who were admitted for their first hip fracture between 2003 and 2013.(120) The orthogeriatric-led FLS reduced post-hip fracture 1-year mortality by 19% and the nurse-led FLS by 16%.(120) A prospective Spanish cohort-study of patients 60 years or older with hip fracture included 357 patients before (2016) and 367 patients after implementation of FLS (2017).(121) There was no effect on 1-year-mortality and no reduction in risk of subsequent fracture with-in 1-year follow-up.(121) Rapp et al. included women and men over 70 years with a fragility fracture

within the last 5 years, and women aged 75-80 regardless of whether they had a previous fracture.(151) That study had a cluster-randomised design where administrative districts were randomised as either intervention-districts or control-districts. They evaluated the effect of a comprehensive fracture prevention program, where 13.6% of the participants had a DXA scan, 3.8% had AOD prescribed, and 51.8% received information on fall prevention, exercise classes and a consultation on "safety in the living environment". With a median follow-up of one year, they found no effect on recurrent fragility fractures as the primary outcome or mortality in the intervention-districts compared to control-districts in a rural area.(151) However, they found a reduction in rate of femoral fractures in the intervention-district compared to the control-district. (151) These results suggest that fall prevention and exercise influence reduction in subsequent fractures. However, a small proportion had AOD prescribed, which may be even a more important component of secondary fracture prevention programs as in the FLS.

The reduction in risk of subsequent fracture in the NoFRACT study is lower than the reduction in subsequent fracture of 18% to 35% in previous studies.(111, 114-119) However, compared to previous studies we included women and men over 50 years with index fractures of any type, except for skull, fingers and toes. These patients had a lower mean age and a lower risk of subsequent fracture rate compared to previous fractures. Furthermore, the intention-to-treat design of the study might have weakened the results compared to a per-protocol design. From the quality assessment data we know that 70% of the patients with a fracture were assessed for osteoporosis or fracture risk and 56% of those had AODs prescribed. This may have weakened the results compared to studies were the whole intervention groups was assessed for osteoporosis.

To our knowledge NoFRACT is the first SW-CRT to evaluate the effect of an FLS on subsequent fracture rates. The SW-CRT design allowed for both a randomised trial design and took into account time trends in fracture rates. Except from the Swedish study from 2020,(116) most studies do not take time trends in fracture rates into account even though many of them were before/after implementation design. The adjustments for time in the NoFRACT study did not change the results. This suggested that the results that the reduction in risk of 12 % for subsequent fracture and a 26% reduction in mortality is associated with the FLS and not a product of time-trends.

6.3 The forearm fracture incidence rates – paper III

The overall findings was that i) the annual number of fractures increased significantly during the study period, ii) incidence rates of forearm fractures in Norway were high, iii) the age-adjusted incidence rate of forearm fractures declined in men, not women, iv) age-adjusted incidence rate of distal forearm fractures declined in both women and men, v) standardised incidence rates of distal forearm fractures were comparable to incidence rates from Finnish and Swedish studies for women and men but lower for women compared to a Danish study.

Previous studies have primarily focused on the incidence of distal forearm fractures. The current study was the first study to evaluate the nationwide incidence of forearm fractures in Norway. Furthermore, we validated the quality of the forearm fracture registrations in the NPR.(140) Distal forearm fractures constituted 76% of the forearm fractures. The mean annual number of all forearm fractures from 2008 to 2019 was 15,148. The increasing total number of forearm fractures is coherent with projection of a double number over the next 10 years.(6) The increasing number of forearm fractures can be explained by an increasing number of elderlies with higher age-adjusted incidences of fractures.(29)

The age-and sex-adjusted incidence rate of distal forearm fractures in adult was 244 per 100,000 PY in Norway from 2009-2014.(16) This was comparable with the results in our study, where mean annual incidence rates was 274 (95% CI 265-284) per 100,000 PY for women and men over 20 years.

The incidence of forearm fractures increased markedly for women over 50 years, and women sustained most of the fractures, as in previous studies.(14, 23, 152, 153) The decline in incidence rates of distal forearm fractures that we reported, is in line with previously proposed decline in incidence of distal forearm fractures seen in Oslo and southern Norway.(23) A regional study from the north-eastern part of Skåne reported decreasing age-adjusted incidence rates of distal forearm fractures from 2011-2016.(22) Furthermore, incidence rates of distal forearm fractures decreased in Stockholm from 2004 to 2010 for adults over 65 years.(26) However, incidence rates of distal forearm fractures in Denmark seem to have plateaued after a decline from 1999-2010, with no change from 2013 to 2019,(19, 27) and no change was detected in Finland from 2015 to 2019.(28)

We calculated standardised incidence rates of distal forearm fractures, because of differences in these demographic compositions between the countries. However, comparisons of incidence rates should still be done cautiously as the studies differed in the methods to distinct incident

from prevalent fractures, age groups included, and study years. The period of the studies extended from 1998/99 to 2019, so incidence rates could also be affected by time-trends. Compared to the Oslo from 1998/99 our rates were lower.(14) However, in that study, Lofthus et al. reviewed medical records and x-ray reports to capture true fractures correctly. They might thereby have captured miscoded fractures that we have missed in the current study. Furthermore, incidence rates of distal forearm fractures have been shown to be higher in urban areas compared to rural, and the lower rates in the current study can be due to time-trends.(8, 153) Crude incidence rates of distal forearm fractures were comparable to studies from southern Norway in 2004-2005 and Akershus, Norway in 2010-2011.(23, 152) However, these studies differed from our study in the way that all fractures were x-ray verified. Standardized incidence rates of distal forearm fractures were comparable to rates in studies from Finland and Sweden, but incidence rates of distal forearm fractures were significantly higher for women in Denmark.(24, 25, 133)

Distal forearm fractures are the most common type of fracture and are highly associated with osteoporosis. (17, 24, 32, 154) The increase in number of fractures will be a burden for society with higher pressure on hospitals, as well as greater economic costs. Forearm fractures are painful for patients and can lead to long-term disability.(74) Furthermore, forearm fractures increase the risk of subsequent fractures.(61, 71, 124) Under-treatment for osteoporosis in patients with a previous forearm fractures have previously been shown in Norway, where, only 11.2% of women and 2.7% of men, used AOD the first year after a first forearm fracture.(102) The high incidence of forearm fractures and the large number of fractures therefore warrants attention. Preventive strategies such as FLS can minimize the risk of future fractures.

7 Conclusions, implications, and further research

In the NoFRACT study, FLS reduced the risk of subsequent fragility fractures, hip fractures, any type of fracture, and mortality in patients with index fracture of any type. Paper III showed that Norway has a high age- and sex-adjusted incidence rate of forearm fractures. The age-adjusted incidence rate of distal forearm fractures declined from 2008-2019, nevertheless, the number of fractures increased significantly.

The high incidence of forearm fractures warrants attention as forearm fractures are costly for both patients and society. Forearm fractures will be an economic burden to society, as the demography changes and the proportion of elderly with higher incidence rates of forearm fractures increase. A distal forearm fracture is an important risk factor for future fractures, still assessment and treatment for osteoporosis in patients with forearm fractures and other types of fragility fractures is undersupplied. From 2005-2012 the usage of AODs the first year after a forearm fracture in Norway was 11.2% for women and 2.7% for men.(102) FLS have been proposed as a solution to reduce the risk of subsequent fractures, with individual fracture risk assessment and treatment with AODs.(73, 85, 99) The NoFRACT study gives evidence that FLS is a useful strategy for secondary fracture prevention. Mapping of the incidence of forearm fractures in Norway can be of help in planning preventive measures such as FLSs on all orthopaedic departments in Norway. The results from the NoFRACT study are important as we still struggle with a gap between recommendations and practice at most of the departments for orthopaedic surgery. This is a challenge in Norway as in many other countries. NoFRACT confirmed findings from previous studies that have suggested that FLS reduces risk of fracture and mortality. One important point in the current FLS is that we treated some patients directly, without further testing, if they had a fracture of the hip, vertebrae or two or more fractures of other types. These results are important arguments as support for establishing FLS led by nurses at all departments for orthopaedic surgery, to increase AOD treatment of patients at the highest risk of fractures. Furthermore, implementation of an FLS can reduce unconscious biases in treatment of patients, for instance men are under-treated to a larger extent than women in Norway, only 4.6% of men compared to 16.9% of women received AODs after a hip fracture.(101) In NoFRACT, assessment and treatment of osteoporosis were offered all women and men over 50 years of age, regardless of age, sex, socioeconomic status, educational level, or country of birth. FLS may therefore reduce the social inequality in health because it does not depend on any awareness or initiative by the fracture patients. This will be investigated in a future study. The FLS in NoFRACT was well received by patients who were invited to the FLS-

intervention, and many of them appreciated to be offered AOD treatment if indicated. However, after the end of the NoFRACT study, not all hospitals have been able to cover the costs to pay personnel to continue FLS as a clinical routine. With the aging population it is increasingly important to prevent fractures. Robust results are very useful to convince the decision makers to give priority to this work.

Further research is warranted to investigate whether the patients receive the secondary prevention (at departments of orthopaedic surgery) as recommended by the society of orthopaedic surgeons. There is still a lack of knowledge in the population about osteoporosis, available treatment, and the benefit by AOD treatment. There is a need to investigate the patient perspectives, on what information they need to understand the importance of osteoporosis, fracture prevention and ensure they feel safe about taking AOD. This is important to improve AOD adherence. Further investigations of the effect of the FLS in different age groups could be done to investigate potential changes in the eligibility criteria for the FLS. Lastly, treatment of forearm fractures, sick leave and morbidity after forearm fractures could be explored in future studies.

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Paper I-III

Paper I

JAMA Network Open

Original Investigation | Orthopedics

Effect of a Fracture Liaison Service on the Rate of Subsequent Fracture Among Patients With a Fragility Fracture in the Norwegian Capture the Fracture Initiative (NoFRACT)
A Trial Protocol

Camilla Andreasen, MD; Lene B. Solberg, PhD; Trude Basso, PhD; Tove T. Borgen, MD; Cecilie Dahl, PhD; Torbjørn Wisløff, PhD; Gunhild Hagen, MPhil; Ellen M. Apalset, PhD; Jan-Erik Gjertsen, PhD; Wender Figved, PhD; Lars M. Hübschle, MD; Jens M. Stutzer, MD; Jan Elvenes, PhD; Ragnar M. Joakimsen, PhD; Unni Syversen, PhD; Erik F. Eriksen, PhD; Lars Nordsletten, PhD; Frede Frihagen, PhD; Tone K. Omsland, PhD; Åshild Bjørnerem, PhD

Abstract

IMPORTANCE Fragility fracture is a major health issue because of the accompanying morbidity, mortality, and financial cost. Despite the high cost to society and personal cost to affected individuals, secondary fracture prevention is suboptimal in Norway, mainly because most patients with osteoporotic fractures do not receive treatment with antiosteoporotic drugs after fracture repair.

OBJECTIVES To improve secondary fracture prevention by introducing a standardized intervention program and to investigate the effect of the program on the rate of subsequent fractures.

DESIGN, SETTING, AND PARTICIPANTS Trial protocol of the Norwegian Capture the Fracture Initiative (NoFRACT), an ongoing, stepped wedge cluster randomized clinical trial in 7 hospitals in Norway. The participating hospitals were cluster randomized to an intervention starting date: May 1, 2015; September 1, 2015; and January 1, 2016. Follow-up is through December 31, 2019. The outcome data were merged from national registries of women and men 50 years and older with a recent fragility fracture treated at 1 of the 7 hospitals.

DISCUSSION The NoFRACT trial is intended to enroll 82 000 patients (intervention period, 26 000 patients; control period, 56 000 patients), of whom 23 578 are currently enrolled by January 2018. Interventions include a standardized program for identification, assessment, and treatment of osteoporosis in patients with a fragility fracture that is led by a trained coordinating nurse. The primary outcome is rate of subsequent fracture (per 10 000 person-years) based on national registry data. Outcomes before (2008-2015; control period) and after (2015-2019; intervention period) the intervention will be compared, and each hospital will act as its own control. Use of outcomes from national registry data means that all patients are included in the analysis regardless of whether they are exposed to the intervention (intention to treat). A sensitivity analysis with a transition window will be performed to mitigate possible within-cluster contamination.

RESULTS Results are planned to be disseminated through publications in peer-reviewed journals and presented at local, national, and international conferences.

CONCLUSIONS By introducing a standardized intervention program for assessment and treatment of osteoporosis in patients with fragility fractures, we expect to document reduced rates of subsequent fractures and fracture-related mortality.

(continued)

Key Points

Question What is the effect of a fracture liaison service on the rate of subsequent fractures?

Findings This trial protocol intends to use merged outcome data from national registers to include 82 000 women and men 50 years and older with a fragility fracture treated in 7 hospitals in Norway in a stepped wedge cluster randomized clinical trial introducing a standardized intervention program. The use of outcome data from national registers, which include all patients in the analysis regardless of whether they are exposed to the intervention (intention to treat), should ensure that outcomes are assessed in a standardized way.

Meaning The design of this trial is intended to overcome the ethical challenges associated with traditional randomized clinical trials and to generate new knowledge on how to improve the current standard of care.

+ Supplemental content

Author affiliations and article information are listed at the end of this article.

Abstract (continued)

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT02536898

JAMA Network Open. 2018;1(8):e185701. doi:10.1001/jamanetworkopen.2018.5701

Introduction

Among women, a prior fracture doubles the risk of a future fracture and multiple fractures increase the risk of future fractures up to 5 times.[1] One-third of fractures occur within the first year and 75% of subsequent fractures after a hip fracture occur within 5 years.[2,3] Hip and vertebral fractures are known to increase mortality, and new data suggest that other major osteoporotic fractures are also associated with a reduction in life expectancy.[4] Treatment of patients with fragility fractures should therefore not only focus on the current fracture but also on preventing future fractures. Even though treatment for osteoporosis is readily available and can reduce the risk of future fractures by 20% to 50%,[5,6] the assessment and treatment for osteoporosis after a fragility fracture has been suboptimal. Two Norwegian studies[7,8] have demonstrated that only 15% of women and 4% of men were treated with antiosteoporotic drugs after a hip fracture,[7] and 11% of women and 3% of men were treated with antiosteoporotic drugs the first year after a forearm fracture.[8] These findings are consistent with those of studies from other countries where less than 20% of patients with a fragility fracture received treatment for osteoporosis.[9,10]

A fracture liaison services (FLS) model of care with a dedicated coordinator and a systematic approach to identify, assess, and treat patients with a fragility fracture for osteoporosis has been introduced in numerous places.[11,12] The FLS programs have been shown to increase the referrals to bone mineral density (BMD) measurements using dual-energy x-ray absorptiometry for screening of osteoporosis.[12] In a Swedish minimal FLS that was coordinated by medical secretaries, the proportion of patients receiving dual-energy x-ray absorptiometry evaluation increased from 8% to 40% and the treatment rate increased from 13% to 32%. Furthermore, individuals who received treatment had a 51% lower risk of subsequent fractures compared with those who did not receive treatment.[13]

Few researchers have studied subsequent fracture rates and mortality as outcomes in studies of the effect of FLS programs.[13-20] In Australia, a 30% reduction in risk of any subsequent fracture and a 40% reduction in risk of major subsequent fractures were shown.[14] In the Netherlands, a significant decrease in mortality of 33% was reported,[15] and in England, a reduction around 20% was found.[16] However, a Swedish study showed no effect of FLS on subsequent fracture rates or mortality, and an Australian study reported the effect of FLS on risk of subsequent fractures and no effect on mortality rates.[13,14] Studies of FLS with subsequent fracture rates and mortality as outcomes are presented in **Table 1**. Although previous FLS studies are of great value, there has, to our knowledge, been no randomized clinical trial on FLS with fracture rates and mortality as outcomes. In a recent observational study,[21] reduced mortality and subsequent fracture risk was shown in individuals who were recommended anti-osteoporotic drugs as part of an FLS program. The authors of that study proposed that traditional randomized clinical trials of FLS are unlikely to be performed given the ethical challenges of randomizing some individuals to less-than-recommended care. Moreover, the FLS program has not been evaluated on a public health scale, and more robust evidence is therefore needed.[11,22,23]

When the Norwegian Capture the Fracture Initiative (NoFRACT) study was designed in 2014, there was no systematic routine or national guideline for the identification and treatment of patients with fragility fractures in Norway. Most patients were offered neither assessment nor treatment for osteoporosis. This gap in care motivated a large-scale evaluation of the effect of introducing a standardized secondary fracture prevention program on subsequent fracture rates and mortality in Norway. The NoFRACT study is, to our knowledge, the first FLS study with a stepped wedge cluster randomized clinical trial design, overcoming the ethical challenges of a traditional randomized clinical

trial. The study may generate new knowledge and provide evidence on how to improve the current standard of care.

The study has aimed to assess the effect of introducing an FLS standardized intervention program for the treatment of osteoporosis in patients with a fragility fracture on subsequent fracture rates (per 10 000 person-years). The study has also assessed the effect of introducing an FLS standardized intervention program for treatment of osteoporosis in patients with a hip fracture on all-cause mortality after hip fracture.

Methods

Study Setting

This trial protocol followed the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) reporting guideline. For largely unknown reasons, Norway is among the countries with the highest incidence rates of forearm and hip fractures worldwide.[24-26] Each year, almost 10 000 Norwegians older than 50 years have a hip fracture, and the annual number of forearm fractures is estimated to be approximately 15 000.[25,27,28] Hip fractures account for almost 20% of fragility fractures,[29] implying a total of approximately 50 000 osteoporotic fractures annually in Norway. Despite a decline in age-standardized hip fracture rates between 1999 and 2013, the total number of hip fractures has increased owing to the aging population.[26,30,31] The ongoing NoFRACT multicenter study is being conducted in the orthopedic departments at the following 7 hospitals in Norway: University Hospital of North Norway, Tromsø; St Olav's University Hospital, Trondheim; Oslo University Hospital, Oslo; Haukeland University Hospital, Bergen; Molde Hospital, Molde; Drammen Hospital,

Table 1. Studies of FLS With Rates of Subsequent Fracture and Mortality as Outcomes

		Intervention vs Control						
Source	Data Source	Study Design	Patients, No.	Women, %	Mean Age, y	Absolute Fracture Rates, %	Rate of Subsequent Fracture Rate, HR (95% CI)	Mortality Rate, HR (95% CI)
Huntjens et al,[17] 2014	*ICD-9* fracture codes, national obituary database (date of death)	FLS vs non-FLS at different hospitals; prospective design	1412 vs 1910	73 vs 70	71.1 vs 69.6	6.7 vs 6.8[a]	1-y follow-up: 0.84 (0.64-1.10); 2-y follow-up: 0.44 (0.25-0.79)	At 2 y: 0.65 (0.53-0.79)
Nakayama et al,[14] 2016	Emergency department (fracture codes)	FLS vs non-FLS at different hospitals; prospective design, intention-to-treat approach	515 vs 416 (103 attended FLS)	75 vs 74	76.6 vs 75.0	12.2 vs 16.8	Any refracture, 3-y follow-up: 0.67 (0.47-0.95); major refracture, 3-y follow-up: 0.59 (0.39-0.90)	HR, 1.17[b]
Hawley et al,[16] 2016[c]	*ICD-10* (hip fracture), Office for National Statistics (mortality)	Pre-FLS and post-FLS; before-after time series design	33 152	78	82.7	4.2	1.03 (0.85-1.26)	At 30 d: 0.80 (0.71-0.91); at 1 y: 0.84 (0.77-0.93)
Axelsson et al,[13] 2016	*ICD-10*, Swedish Population Register (death information)	Pre-FLS vs post-FLS; prospective design with historic controls	2713 vs 2616	73 vs 74	76.1 vs 76.7	8.4 vs 8.3	0.95 (0.79-1.14)	0.88 (0.76-1.03)
Huntjens et al,[15] 2011	*ICD-9*, national obituary database	Pre-FLS vs post-FLS	1920 vs 1335	75 vs 73	70.8 vs 71.9	9.9 vs 6.7	2-y follow-up: 0.65 (0.51-0.84)	At 2 y: 0.67 (0.55-0.81)
Van der Kallen et al,[18] 2014	Diagnosis codes	FLS nonattendees vs FLS attendees; prospective design	220 vs 214	77 vs 79	74 vs 72	18.6 vs 6.5	2-y follow-up: 18.6 vs 6.5[d]	NA
Astrand et al,[19] 2012	Questionnaire	Pre-FLS vs post-FLS; historic controls	306 vs 286	72 vs 76	NA	29 vs 18	6-y follow-up: 0.58 (0.39-0.89)	17 vs 12[a,d]
Lih et al,[20] 2011	Not mentioned	Nonattendees vs attendees; MTF service; prospective controlled observational design	156 vs 246	75 vs 83	65.9 vs 66.4	19.7 vs 4.1	Median 38-mo follow-up: 5.3 (2.71-11.6)	NA

Abbreviations: FLS, fracture liaison service; HR, hazard ratio; *ICD-9, International Classification of Diseases, Ninth Revision*; *ICD-10, International Statistical Classification of Diseases and Related Health Problems, Tenth Revision*; MTF, minimal trauma fracture; NA, not applicable.

[a] Nonsignificant.

[b] The 95% CI was not provided in the original article.

[c] Because of the study design, data are shown for 1 group.

[d] Absolute rates because HRs and 95% CIs were not calculated.

Drammen; and Bærum Hospital, Bærum. These hospitals represent both smaller and larger hospitals and are geographically spread across Norway. The NoFRACT study has received approval from the Regional Committee for Medical and Health Research Ethics, Region for South Eastern Norway, for the merging of data from national registers and exemption from obtaining consent from the patients with fractures. All data will be deidentified, and the code will be retained by the Norwegian Patient Registry (NPR).

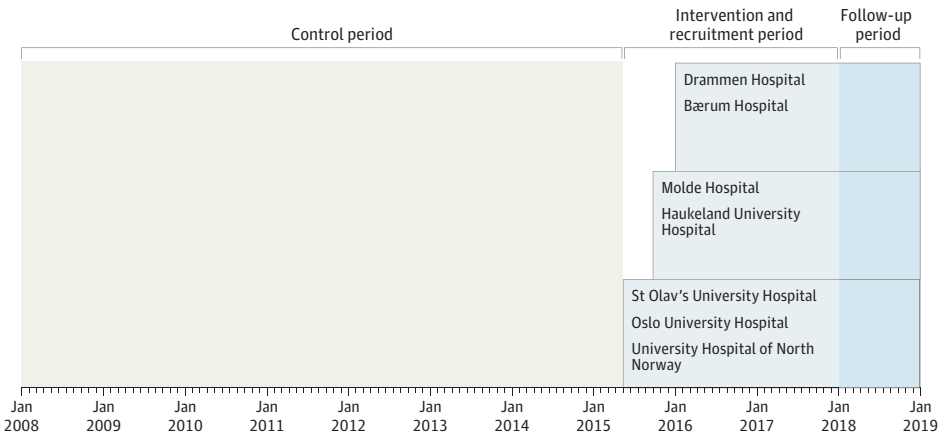
Trial Design, Randomization, and Recruitment

The hospitals were randomized to intervention starting date in a stepped wedge cluster randomized, open cohort design.[32,33] The design was chosen because FLS has been shown to be of more benefit than harm, and this particular design is efficient for evaluating interventions that have previously been found to be effective in individually randomized studies. We sought to evaluate the effect of the intervention in a public health setting for implementation in clinical practice. In the design, the intervention is introduced to each cluster at regular time intervals. Each hospital acts as its own control, providing outcome data from before the intervention (2008-2015; control period) and after the intervention (2015-2019; intervention period). Randomization by lottery was conducted 8 weeks before the study start by an independent organization, the Norwegian Osteoporosis Association. The intervention was introduced with 4-month intervals between the clusters, and the 7 hospitals were divided into 3 sequences consisting of 2 to 3 clusters (hospitals) in each step. University Hospital of North Norway, St Olav's University Hospital, and Oslo University Hospital were scheduled to start the intervention on May 1, 2015; Haukeland University Hospital and Molde Hospital on September 1, 2015; and Drammen Hospital and Bærum Hospital on January 1, 2016 (**Figure 1**). The recruitment phase has been ongoing from May 1, 2015, through December 31, 2018, with follow-up planned throughout December 31, 2019. Different patients were included at each step but subsequently followed up throughout the study period (open cohort design). The observation time in the intervention period (2015-2019) will range from 12 to 56 months for each of the patients in the study (unless an outcome or censoring takes place before the end of follow-up).

Eligibility Criteria

Women and men 50 years and older with a recently diagnosed low-energy fracture who were admitted at 1 of the 7 hospitals were included, either while in the hospital or as outpatients within 6 weeks after the fracture. Patients with fractures of fingers, toes, skull, or face were ineligible. The

Figure 1. Norwegian Capture the Fracture Initiative (NoFRACT) Stepped Wedge Cluster Randomized Clinical Trial Design



The 7 hospitals were randomized for the order of the starting dates and divided into 3 sequences. The intervention was introduced stepwise with 4-month intervals. The intervention period started on May 1, 2015, and will continue through December 31, 2018, with follow-up through December 31, 2019. The University Hospital of North Norway was scheduled to start on May 1, 2015, but was delayed for 5 months and started on October 1, 2015.

very fragile patients, who were not expected to live long enough for the intervention to take effect as judged by the treating physician, will not receive the intervention. However, they will remain in the statistical analyses (intention to treat).

Study Intervention

The intervention is a standardized program for identification, assessment, and treatment of osteoporosis in patients with a recently diagnosed low-energy fracture (a fracture occurring after a fall from standing height or less) and is based on the FLS model of care (**Figure 2**).

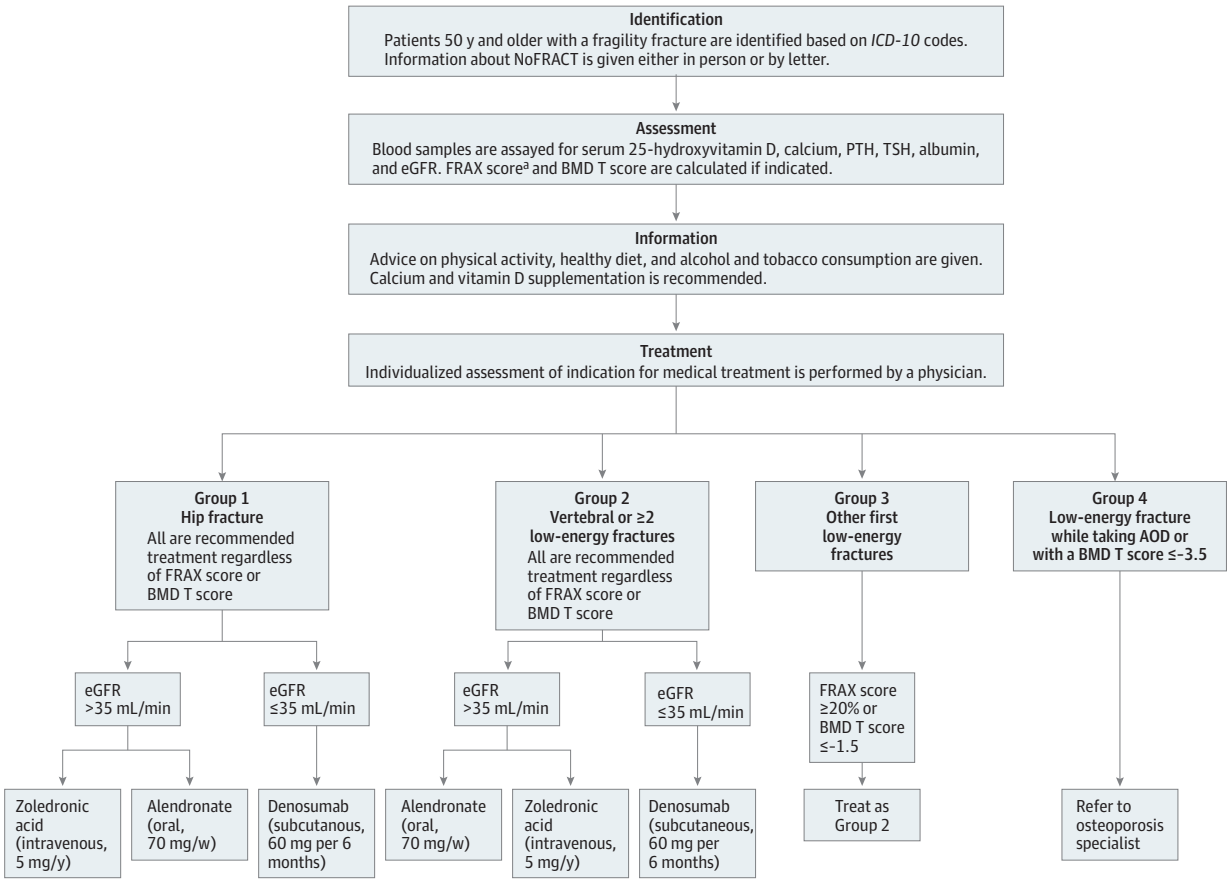
Identification

The coordinating nurse identifies the patients based on the hospital *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10)* codes and eligibility criteria and provides information about the project either in person or in a letter sent to recently discharged inpatients and outpatients.

Assessment

Blood samples are obtained from the patients with fractures within 6 weeks of the index fracture to rule out common causes for secondary osteoporosis. The blood samples are assayed for serum levels of 25-hydroxyvitamin D, calcium, parathyroid hormone, thyroid-stimulating hormone, albumin, and

Figure 2. Application of the Standardized Intervention Program in the Norwegian Capture the Fracture Initiative (NoFRACT) Trial



AOD indicates antiosteoporosis drugs; BMD, bone mineral density; eGFR, estimated glomerular filtration rate; *ICD-10*, *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision;* PTH, parathyroid hormone; and TSH, thyroid-stimulating hormone.

[a] The Fracture Risk Assessment Tool (FRAX) is used to calculate the 10-year probability of major osteoporotic fracture (score is given as a percentage; a higher percentage indicates higher probability of fracture).

creatinine. Kidney function is assessed using estimated glomerular filtration rate (eGFR).[34] The BMD is measured using dual-energy x-ray absorptiometry of both hips and spine, and BMD T score is calculated. The 10-year probability of major osteoporotic fracture is calculated using the Fracture Risk Assessment Tool (FRAX; score is given as a percentage, with a higher percentage indicating a higher probability of fracture).[35]

Information

The coordinating nurse informs the patients on the importance of bone fragility and provides general lifestyle advice on physical activity, healthy diet, and tobacco and alcohol consumption according to national guidelines. All patients are recommended sufficient intake of calcium and vitamin D through diet or supplementation (500-1000 mg of calcium and 800 IU of vitamin D daily). Patients are also referred to fall prevention programs at the hospital or in primary care if the nurse finds this protocol to be relevant.

Treatment

Antiosteoporotic drugs are offered to 4 groups of patients. In group 1, patients with hip fracture are offered treatment regardless of BMD T score or FRAX score. The primary drug of choice for patients with hip fracture is (1) intravenous zoledronic acid (5 mg per year) to evade compliance problems, (2) oral alendronate (70 mg per week), or (3) subcutaneous denosumab (60 mg every 6 months).

In group 2, patients with vertebral fracture or 2 or more low-energy fractures are offered treatment regardless of BMD T score or FRAX score with (1) oral alendronate (70 mg per week), (2) intravenous zoledronic acid (5 mg per year), or (3) subcutaneous denosumab (60 mg every 6 months).

In group 3, patients with their first low-energy fracture are offered dual-energy x-ray absorptiometry for assessment of BMD T score, FRAX score, or both. The same treatment as in group 2 is offered to those with a BMD T score greater than −3.5 and less than or equal to −1.5 or FRAX score of major osteoporotic fracture of 20% or more.

In group 4, patients with a BMD T score of −3.5 or less or a subsequent low-energy fracture while taking anti-osteoporotic drug treatment for more than 1 year are referred to an osteoporosis specialist for consideration of bone anabolic treatment with teriparatide.

All patients are individually evaluated and treated according to comorbidities and kidney function. Bisphosphonates (alendronate or zoledronic acid) are the drugs of choice unless the patient had an eGFR of 35 mL/min or less; those patients are offered denosumab treatment unless they have an eGFR of 20 mL/min or less or any other contraindication was present. Patients with elevated serum levels of parathyroid hormone and calcium are referred to an endocrinologist, whereas patients with smaller deviations in those levels are followed up for 2 to 4 weeks after treatment initiation in primary care, as are patients with elevation of thyroid-stimulating hormone levels.

Length of treatment is dependent on the type of drug. For alendronate, a treatment break is recommended after 5 years; for zoledronic acid, a treatment break is recommended after 3 years; and for denosumab, no treatment break is recommended.

Adherence to the Protocol and to the Intervention

The coordinating nurses at the NoFRACT hospitals underwent training in FLS with a well-trained nurse and physician to ensure standardization of the program. The University Hospital of North Norway was scheduled to start on May 1, 2015, but was delayed for 5 months and started on October 1, 2015. All other hospitals initiated the intervention on the date as scheduled.

The patients who were prescribed treatment with antiosteoporotic drugs were offered follow-up with the coordinating nurse. After 3 months, a phone consultation was performed to rule out misunderstandings, answer questions, and take care of potential adverse events. The close follow-up was conducted to improve the adherence to treatment. After 12 months, the patients were again offered a phone consultation or an appointment with a nurse. Each patient and their general

practitioner were advised concerning length of treatment, and the patient could be referred for a reassessment after 2 to 3 years to decide further treatment.

Potential Harm From the Intervention

Exposure to the intervention is associated with minimal discomfort; however, blood samples are obtained at baseline (start of the intervention), during which some patients may experience a slight discomfort. Dual-energy x-ray absorptiometry is a painless imaging modality with a modest dose of radiation.[36] The most common adverse effects of antiosteoporotic drugs are muscle pains and gastrointestinal symptoms, the latter of which are caused by oral bisphosphonates.[37] Intravenous treatment with zoledronic acid is associated with transient hypocalcemia and influenzalike symptoms. In addition, bisphosphonates are rarely associated with risk of osteonecrosis of the jaw and atypical femoral fracture.[37] The patients were informed of potential adverse effects from the treatment.

Study Outcomes

The primary study outcome is change in the rate of subsequent fracture (per 10 000 person-years) for patients with the following *ICD-10* codes: S22 (rib[s], sternum, and thoracic spine), S32 (lumbar spine, pelvis), S42 (shoulder, upper arm), S52 (forearm), S62 (wrist, hand), S72 (femur), S82 (patella, lower leg, and ankle), and S92 (foot). The secondary study outcome is all-cause mortality among patients with the following *ICD-10* codes: S72.0-S72.2 (hip fracture).

Sample Size Determination

Initially, the plan was to include 87 000 patients based on sample size calculations performed before starting the trial (during 2008-2017) (ie, approximately 9600 patients each year). Local counting of patients exposed to the NoFRACT intervention at the 7 Norwegian hospitals during 2015-2017 showed that approximately 7500 patients with fracture had been included annually. Because the recruitment of patients had been somewhat lower than expected, a decision was made to continue the recruitment for 1 additional year throughout 2018, with data obtained from registers throughout 2019 (to achieve at least 1 year of observation time for all patients). There are 4 months between the steps in our design (3 steps per year) at the 7 hospitals; this design gives a mean cluster size of 357 patients (7500/[7 × 3] = 357). Because the baseline data from patients will be used for a total of 11 calendar years (2008-2018), a revised estimate of the number of patients who will be included is 82 467 (357 × 7 × 3 × 11 = 82 467; approximately 56 000 patients in the control period and 26 000 in the intervention period). Power calculations using the "steppedwedge" command in Stata, version 15 (StataCorp), show that we have 80% power to detect a relative risk of 0.73 for any type of subsequent fracture in the intervention period vs control period. This figure assumes inclusion of 82 467 patients with fracture (any fracture type), intracluster correlation of 0.03, and cluster size of 357. The intracluster correlation was calculated as in a previous study.[3] In these calculations, the proportions of subsequent fracture in the intervention and control periods were estimated to be 6% and 9%, respectively, after 1.5 years based on previous FLS studies.[13,14,17] Estimates from the Swedish study by Axelsson et al[13] (after 0.9 years of follow-up: 6.6% in the treated group vs 8.8% in the untreated group; relative risk, 0.75) were given the most weight because Sweden, similar to Norway, has high fracture rates[24]; however, the incidence of fractures estimated in other relevant studies were also considered.[3,27,38,39]

Regarding hip fracture risk among patients with a first fracture of any type, power calculations give a relative risk of 0.52 in the intervention vs control periods, assuming 80% power, inclusion of 82 467 patients with fractures, proportions of patients with a subsequent hip fracture of 3.0% in the control period and 1.6% in the intervention period, an intracluster correlation of 0.03, and a cluster size of 357.[3]

Data Sources and Collection

Outcome, time at risk, and potential confounding factors have been obtained since January 1, 2008, and will continue to be collected through December 31, 2019, from the following national registries: the NPR, National Population Register, Statistics Norway, and Norway Control and Reimbursement of Healthcare Claims (KUHR) (**Table 2**). The NPR provides data on patients with fractures treated at Norwegian hospitals. Fracture diagnoses other than hip fracture (which is always treated in hospitals) is also complemented by the KUHR database, which comprises fractures treated by primary care physicians and emergency units in rural and semirural areas.

Validity

The use of registry data are highly dependent on the quality of the registries. The accuracy of hip fracture diagnosis in the NPR has been evaluated and found to be 93.5%.[40] A study of the distribution and degree of overlap of fracture diagnoses in the NPR and KUHR will be performed. Ahead of our main analysis, the accuracy of the diagnosis of forearm fracture will also be evaluated in a separate validation study that includes fractures from hospitals (registered in the NPR) and from the primary health care service (registered in the KUHR).

Data Management

All data will be deidentified by replacing the personal identification number with a project-specific identification number for each individual. The code (personal identification vs project-specific identification) will be retained by the NPR. The data will be securely stored at a protected platform for research at the University of Oslo, Services for Sensitive Data, which meets all Norwegian law requirements. Data will be available only to collaborators with the approval by the Regional Committee for Medical and Health Research Ethics, Region South Eastern Norway. All data management (eg, quality control and linking of data sources) will be performed within the Services for Sensitive Data.

Data Analysis Plan

Outcome data from the control period and intervention period will be compared. The date of the index fracture (first fracture in the trial period) determines whether a patient's data will be included in the control or intervention period. The study will use time-to-event analysis, in which time at risk of subsequent fractures will be calculated based on first fracture dates (hospitalization dates or primary health care treatment dates), dates of migration or event occurrence (death from the National Population Register or subsequent fracture from the NPR), or the end of the study (December 31, 2019). Using calendar time as the scale will allow observation of secular changes in subsequent fracture risk over time, and if necessary, differences in secular trends between hospitals will be considered by including an interaction term between cluster and time. Clustering by hospital will be included as random effects in mixed models to estimate incidence rate ratios with 95% CIs. A uniform correlation structure is assumed,[41] with no decay in the cluster autocorrelation. All patients treated for relevant fractures and residing in a municipality belonging to 1 of the 7 hospitals after initiation of

Table 2. National Registries Used for Outcome Assessment in the Norwegian Capture the Fracture Initiative (NoFRACT) Study

Registry	Variable	Type of Fractures
Norwegian Patient Registry	Sex, birth year, hospital, hospitalization dates, municipality of residence, treatment level, surgical procedure codes, and Charlson comorbidity index	Fractures treated in hospitals
National Population Register	Dates of migration and death, marital status, and country of birth	All fractures
Statistics Norway	Education level	All fractures
Norway Control and Reimbursement of Healthcare Claims	*ICPC-2* diagnosis codes L72-L76, including subgroup	Fractures treated in primary care

Abbreviation: *ICCP-2, International Classification of Primary Care, 2nd ed.*

the intervention will be allocated to the intervention group irrespective of exposure to the intervention (intention to treat). Because risk of subsequent fracture varies by follow-up time and fracture type,[3,39] additional analyses will be performed in which the same maximum follow-up time (1 year) after the index fracture will be used for patients in the control period.

The need for a transition period (period for the intervention to be established) to minimize within-cluster contamination will be explored in sensitivity analyses. The pattern of missing data will be examined, and if necessary, multiple imputation will be performed based on the collected exposure data, covariates, outcome, and intracluster correlation. Analyses will be stratified by sex, and subsequent fracture rates and mortality rates in women and men will be compared. The analyses will be adjusted for potential confounders, such as age, education, and comorbidity (Charlson index score).

Trial Status

At the beginning of January 2018, there were 23 578 patients enrolled in the intervention period of the NoFRACT study of the approximately 26 000 patients planned.

Patient and Public Involvement

The development of NoFRACT was motivated by previous studies that showed undertreatment of osteoporosis in patients with fragility fractures.[7-10] Patients were not involved in the initial development of the study design, conduct, and recruitment. However, 2 patients with a previous fracture who have been receiving antiosteoporotic drugs have been involved in the later stages of the study and contributed to the development of new research questions. The patients were recruited through the NoFRACT network and were interviewed regarding preferences and experiences; they also commented on the trial protocol. Patients' priorities, experience, and preferences have also been discussed in public meetings.

Dissemination Plan

The dissemination plan includes publication of positive, negative, and inconclusive results in peer-reviewed Norwegian and international scientific journals. Primary and secondary outcomes will be presented in separate papers. Authorship for the scientific papers will be settled according to the Vancouver protocol and the International Committee of Medical Journal Editors recommendations. The results from the study will be presented at national and international academic meetings. The protocol and journal publications will be made available to the public; however, because of strict protection of privacy under Norwegian law, individual-level data sets can only be shared if approved by the Regional Committee for Medical and Health Research Ethics.

The results from the study will be disseminated to the public through newspapers, television, public meetings, and social media in collaboration with 2 patient advisors. To reach the patients more directly, the results will be communicated to treating physicians and hospital staff and through patient organization. Implementation of research results into clinical practice is important. It is therefore necessary to communicate research results and clinical treatment strategies to decision makers to ensure that best clinical practice is implemented and made equally available for the patients in Norway and worldwide.

Conclusions

By introducing a standardized intervention program for assessment and treatment of osteoporosis in patients with fragility fractures, we expect to document reduced rates of subsequent fractures and fracture-related mortality.

ARTICLE INFORMATION

Accepted for Publication: October 17, 2018.

Published: December 7, 2018. doi:10.1001/jamanetworkopen.2018.5701

Corresponding Author: Camilla Andreasen, MD, Department of Orthopedic Surgery, University Hospital of North Norway, Postbox 100, 9038 Tromsø, Norway (camilla.andreasen@uit.no).

Author Affiliations: Department of Orthopedic Surgery, University Hospital of North Norway, Tromsø, Norway (Andreasen, Elvenes); Department of Clinical Medicine, Arctic University of Norway, Tromsø, Norway (Andreasen, Elvenes, Joakimsen, Bjørnerem); Division of Orthopedic Surgery, Oslo University Hospital, Oslo, Norway (Solberg, Nordsletten, Frihagen); Department of Orthopedic Surgery, St Olav's University Hospital, Trondheim, Norway (Basso); Department of Rheumatology, Vestre Viken Hospital Trust, Hospital of Drammen, Drammen, Norway (Borgen); Department of Community Medicine and Global Health, Institute of Health and Society, University of Oslo, Oslo, Norway (Dahl, Wisløff, Omsland); Department of Infectious Disease Epidemiology and Modelling, Norwegian Institute of Public Health, Oslo, Norway (Wisløff); Department of Reviews and Health Technology Assessments, Norwegian Institute of Public Health, Oslo, Norway (Hagen); Bergen Group of Epidemiology and Biomarkers in Rheumatic Disease, Department of Rheumatology, Haukeland University Hospital, Bergen, Norway (Apalset); Department of Global Public Health and Primary Care, University of Bergen, Bergen, Norway (Apalset); Department of Orthopedic Surgery, Haukeland University Hospital, Bergen, Norway (Gjertsen); Department of Clinical Medicine, University of Bergen, Bergen, Norway (Gjertsen); Department of Orthopedic Surgery, Bærum Hospital, Vestre Viken Hospital Trust, Bærum, Norway (Figved); Department of Orthopedic Surgery, Vestre Viken Hospital Trust, Hospital of Drammen, Drammen, Norway (Hübschle); Department of Orthopedic Surgery, Møre and Romsdal Hospital Trust, Molde Hospital, Molde, Norway (Stutzer); Department of Medicine, University Hospital of North Norway, Tromsø, Norway (Joakimsen); Department of Endocrinology, St Olav's University Hospital, Trondheim, Norway (Syversen); Department of Clinical and Molecular Medicine, Norwegian University of Science and Technology, Trondheim, Norway (Syversen); Department of Endocrinology, Morbid Obesity and Preventive Medicine, Oslo University Hospital, Oslo, Norway (Eriksen); Department of Clinical Medicine, University of Oslo, Oslo, Norway (Eriksen, Nordsletten); Department of Obstetrics and Gynecology, University Hospital of North Norway, Tromsø, Norway (Bjørnerem).

Author Contributions: Drs Dahl and Omsland had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Andreasen, Solberg, Basso, Borgen, Dahl, Wisløff, Hagen, Gjertsen, Figved, Stutzer, Joakimsen, Syversen, Eriksen, Nordsletten, Frihagen, Omsland, Bjørnerem.

Acquisition, analysis, or interpretation of data: Solberg, Wisløff, Apalset, Hübschle, Stutzer, Elvenes, Joakimsen, Eriksen.

Drafting of the manuscript: Andreasen, Solberg, Basso, Stutzer, Omsland, Bjørnerem.

Critical revision of the manuscript for important intellectual content: Solberg, Basso, Borgen, Dahl, Wisløff, Hagen, Apalset, Gjertsen, Figved, Hübschle, Stutzer, Elvenes, Joakimsen, Syversen, Eriksen, Nordsletten, Frihagen, Omsland, Bjørnerem.

Statistical analysis: Dahl, Wisløff, Joakimsen.

Obtained funding: Solberg, Basso, Borgen, Hagen, Syversen, Nordsletten, Frihagen, Omsland, Bjørnerem.

Administrative, technical, or material support: Andreasen, Solberg, Basso, Borgen, Figved, Stutzer, Elvenes, Syversen, Frihagen, Omsland, Bjørnerem.

Supervision: Dahl, Wisløff, Gjertsen, Figved, Joakimsen, Eriksen, Nordsletten, Frihagen, Omsland, Bjørnerem.

Conflict of Interest Disclosures: Dr Wisløff reported personal fees from Biogen and Amgen. Ms Hagen reported other funding from Pfizer. Dr Figved reported personal fees from Zimmer Biomet and Ortomedic AS Norway. Dr Joakimsen reported fees for lectures held on topics other than osteoporosis and/or epidemiology of fractures paid by several stakeholders: universities and colleges, patient organizations, and pharmaceutical companies (AstraZeneca, NovoNordisk, and Eli Lilly and Company). Dr Syversen reported personal fees from Eli Lilly and Company, MSD, Amgen, and Nycomed. Dr Frihagen reported grants from Eli Lilly and Company, Takeda, and Amgen. No other disclosures were reported.

Funding/Support: This work was supported by grant 243852 from the Regional Health Authorities, grant 14083 from Northern Norway Regional Health Authority, grant 19003007 from Vestre Viken Hospital Trust, grant 46055600-51 from St Olav's University Hospital, and grant 2017032 from South-Eastern Norway Regional Health Authority.

Role of the Funder/Sponsor: The funding organizations had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Data Sharing Statement: See Supplement 2.

Additional Contributions: The patient advisors provided supportive comments on the study and helped with development of new research questions. The following individuals contributed to the idea and design of the project: Lene B. Solberg, PhD; Frede Frihagen, PhD; Lars Nordsletten, PhD; Erik F. Eriksen, PhD; Ruth Aga, MD; Ida Lund, MD; Janne B. Høglund, BA; Ingvild Hestnes, BA; Ellen Johansson, BA; Mette B. Larsen, BA; Elise B. Vesterhus, BA (all from Oslo University Hospital); Tone K. Omsland, PhD; Cecilie Dahl, PhD (both from University of Oslo); Torbjørn Wisløff, PhD; Gunhild Hagen, MPhil (both from Norwegian Institute of Public Health); Wender Figved, PhD; Ellen T. Langslet, MD; Merete Finjarn; BA (all from Bærum Hospital); Tove T. Borgen, MD; Lars M. Hübschle, MD; May-Britt Stenbro, BA; Hanne L Hoelstad, BA (all from Drammen Hospital); Jan-Erik Gjertsen, PhD; Ellen M. Apalset, PhD; Mariann Hansen, BA (all from Haukeland University Hospital); Jens M. Stutzer, MD; Charlotte Råmkes, BA; Solveig Solberg, BA; Lasse Ørsal, BA (all from Molde Hospital); and Trude Basso, PhD; Unni Syversen, PhD; Sølvi Liabakk, BA; Nina Raaness Larsen, BA; Kristine A. Haugen, BA; Gry M. Torstensen, BA; Tine Dybdahl, BA; Elly Nordstrand, BA; Åshild Bjørnerem, PhD; Camilla Andreasen, MD; Ragnar M. Joakimsen, PhD; Jan Elvenes, PhD; Anita Kanniainen, BA; May Greta Pedersen, BA (all from University Hospital of North Norway). International collaborators: David Marsh, PhD (Royal National Orthopedic Hospital, Stanmore, UK); Kristina Åkesson, PhD (Skåne University Hospital, Malmø, Sweden); Stephen Gallacher, PhD (Southern General Hospital, Glasgow, UK); and Henrik Palm, PhD (Hvidovre Hospital, Copenhagen, Denmark). They did not receive compensation for their contributions.

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SUPPLEMENT 1.
Trial Protocol

SUPPLEMENT 2.
Data Sharing Statement

Paper II

Paper III