EUROPEAN CONSENSUS STATEMENT ON THE DIAGNOSIS AND MANAGEMENT OF OSTEOPOROSIS IN CHRONIC KIDNEY DISEASE STAGES G4 to G5D

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ABSTRACT

Controlling the excessive fracture burden in patients with chronic kidney disease (CKD) stage G4-G5D remains an impressive challenge. The reasons are twofold. First, the pathophysiology of bone fragility in patients with CKD G4-G5D is complex and multifaceted, comprising a mixture of age-related (primary male/postmenopausal), drug-induced and CKD-related bone abnormalities. Second, our current armamentarium of osteoporosis medications has neither been developed for, nor adequately studied in, patients with CKD G4-G5D, partly related to difficulties in diagnosing osteoporosis in this specific setting and fear of complications. Doubts about the optimal diagnostic and therapeutic approach fuel inertia in daily clinical practice. The scope of the present consensus paper is to review and update the assessment and diagnosis of osteoporosis in patients with CKD G4-G5D, and to discuss the therapeutic interventions available and the manner in which these can be used to develop management strategies for the prevention of fragility fracture. As such, it aims to stimulate a cohesive approach to the management of osteoporosis in patients with CKD G4-G5D, to replace current variation in care and treatment nihilism.

SUMMARY OF MAIN RECOMMENDATIONS ON THE DIAGNOSIS AND MANAGEMENT OF OSTEOPOROSIS IN CHRONIC KIDNEY DISEASE G4 TO G5D

Diagnosis of osteoporosis in CKD

1. Osteoporosis is a condition characterized by low bone mass and microarchitectural and qualitative bone deterioration that leads to bone fragility and fracture susceptibility.

2. The operational definition of osteoporosis is based on an areal bone mineral density (BMD) assessed by dual energy X-ray absorptiometry (DXA) at spine or hip below -2.5 SD from the BMD in young female adults (T-score).

Risk factors for fragility fractures

1. Clinical risks factors for osteoporosis in CKD patients comprise traditional risk factors including older age, female sex, low body mass index, fragility fracture history, glucocorticoid treatment and CKD-specific risk factors such as long dialysis duration.

2. Bone mineral density (BMD) as assessed by dual energy X-ray absorptiometry (DXA) predicts fractures in patients with CKD G4-G5D. However, DXA most probably underestimates the actual fracture risk in patients with CKD G4-G5D, as it does not account for impaired bone quality. The consistency of the risk prediction across stages of disease and degree of PTH control remains to be documented.

Assessment of fracture risk

1. In patients with CKD G4-G5D, DXA may be considered in postmenopausal women or males aged > 50 yrs. Routine DXA testing (screening) in all CKD G4-G5D patients is not supported by current evidence.

2. The hip and the lumbar spine are the primary skeletal site to evaluate BMD by DXA.

3. Forearm may be included in the DXA evaluation skeletal site panel, but one should be aware of operator dependent variability and/or potential bias by AV fistula.

4. Trabecular bone score and alternative imaging techniques need further clinical evaluation pending clinical implementation.

5. Vertebral fracture assessment (VFA), and/or lateral spine imaging, is recommended in all patients undergoing DXA evaluation and in patients with history of ≥ 4 cm height loss, kyphosis, or recent or current long-term oral glucocorticoid therapy. Imaging should include the abdominal aorta for determination of vascular calcification.

6. FRAX® predicts fracture probability in all CKD stages. Additional evidence is required to define whether further arithmetic adjustments to conventional FRAX estimates have to be made with knowledge of advanced CKD.

8. Non-kidney-retained bone turnover markers, especially bone-specific alkaline phosphatase, may be useful for fracture risk prediction in CKD G4-G5D, awaiting further confirmation.

Intervention thresholds for pharmacological therapy

1. CKD patients aged > 50 yrs with a prior fragility fracture (major osteoporotic fracture, MOF) may be considered for treatment without the need for further BMD assessment.

2. In absence of MOF, a DXA T-score threshold ≤ -2.5 at the lumbar spine or hip is recommended, recognizing a higher threshold of -2.0 or -1.5 may be more appropriate.

3. FRAX® country specific intervention thresholds are appropriate in CKD patients.

Non-pharmacological intervention

1. A sufficient supply of calcium should be guaranteed (800 -1200 mg/d, preferentially through diet) and vitamin D stores should be repleted according to osteoporosis and CKD-MBD guidelines.

2. Regular weight-bearing exercise should be advised, tailored to the needs and abilities of the individual patient.

3. Falls risk need to be evaluated regularly and acted upon.

Pharmacological intervention

1. CKD-MBD therapy should be optimized according to current guidelines before considering specific osteoporosis management.

2. Metabolic disturbances linked to bone fragility (acid-base, uremic toxicity) should be controlled at all times.

3. Risks and benefits of available pharmacological interventions need to be balanced at the individual level and discussed with the patient. Formal informed consent may be required when considering off-label use.

4. Evolving evidence indicates that antiresorptive agents may be effective in advanced CKD and that vascular and skeletal risks are not excessively high.

5. Renal risks of bisphosphonates are poorly explored in patients with CKD G4-G5D and call for caution.

6. Denosumab has no risk of worsening CKD but risk of severe hypocalcemia with denosumab is increased in CKD and needs to be addressed by concomitant vitamin D and calcium supplementation.

7. Withdrawal of denosumab therapy may be associated with an increased risk of vertebral fracture rate.

Monitoring

1. Non-kidney-retained bone turnover markers (BTMs), such as bone specific alkaline phosphatase, intact procollagen type I N-propeptide, and tartrate-resistant acid phosphatase 5b, should be preferentially monitored in CKD patients.

2. Monitoring of BTMs may inform on the early therapeutic response.

3. Monitoring of BTMs after therapy withdrawal (offset of effect) may inform on the need for reintroduction.

4. Repeat DXA informs on the long-term treatment effect on BMD. The time interval when treatment effect can be detected may vary depending on treatment modality and underlying type of renal osteodystrophy.

Systems of care

1. Coordinator-based Fracture Liaison Services (FLS) should be considered to systematically identify and guide CKD patients with fragility fractures, in close collaboration with nephrologists. The (cost-)effectiveness of FLS has been established in the general population.

INTRODUCTION

Chronic Kidney Disease (CKD) is defined by the Kidney Disease: Improving Global Outcomes (KDIGO) CKD guideline as abnormalities of kidney structure or function, present for more than 3 months, with implications for health. As much as 10–15% of the adult population is affected worldwide. The NKF/K-DOQI (National Kidney Foundation/Kidney-Disease Outcomes Quality Initiative) has classified CKD into five stages using thresholds of estimated glomerular filtration rate (eGFR). The prevalence of advanced CKD, defined as CKD G4-G5D (corresponding to an eGFR< 30 ml/min 1.73m²), is estimated at 0.5-1% [1;2]. In 2010, 284 individuals per million population are estimated to be undergoing maintenance dialysis (CKD G5D) throughout the world. This number is expected to increase, paralleling the rapid global rise of chronic cardiometabolic diseases[3]. Disturbances in mineral and bone metabolism occur early in the course of CKD to become almost universal in patients with advanced disease. The term CKD-Mineral and Bone Disorder (CKD-MBD) is currently used to describe a broader clinical syndrome that develops as a systemic disorder of mineral and bone metabolism due to CKD, which is manifested by abnormalities in bone and mineral metabolism and/or extra-skeletal calcification. CKD-MBD associates with fractures and cardiovascular morbidity and mortality[4].

Osteoporosis is a condition characterized by low bone mass and/or qualitative bone deterioration that leads to bone fragility and fracture susceptibility[5].The economic and societal burden of fragility fractures is massive, previously estimated at 37 billion euros per year in 27 European countries alone, and is set to rise owing to an increasing skew towards an older population. Over the last 3 decades, the ability to predict those at risk has developed enormously through the use of fracture prediction tools and an increasing understanding of scanning modalities, such as dual-energy X-ray absorptiometry (DXA). Alongside, the armamentarium to tackle osteoporosis has continued to expand. Against this background, the observation of a huge treatment gap between those at risk of fracture and those receiving treatment for the prevention of fragility fractures, is large and quite remarkable [6].

Both CKD and osteoporosis may evolve subclinically over years, with renal failure (imminent need for dialysis) and fracture, respectively, often being the presenting scenario. CKD and osteoporosis are common diseases of the elderly and often go hand in hand. Incorporated in CKD G4-G5D is a state of impaired bone quantity[7-13]and quality[14] which associates with increased fracture risk[15]. E.g. patients with CKD G5D show a non-vertebral fracture risk that is 4-6 fold higher than the fracture risk of age and gender matched controls[16;17]. Fractures are a major cause of morbidity and, compared to CKD patients without fractures, those with fractures experience a multifold increased risk of mortality[18;19].

While osteoporosis care in patients with CKD G1-G3, is not different from the general population, as long as there are no biochemical abnormalities suggesting the presence of CKD-MBD, osteoporosis care in patients with CKD G4-G5D remains a major challenge. The complexity of the pathophysiology of bone fragility in these patients as well as the lack of data on efficacy and safety of osteoporosis medications in patients with CKD G4-G5D[20] fuel diagnostic and therapeutic inertia [21;22]. Abovementioned treatment gap may thus be hypothezised to be even wider in patients with CKD G4-G5D.

The scope of the present consensus paper is to review and update the assessment and diagnosis of osteoporosis in patients with CKD G4-G5D, and to discuss the therapeutic interventions available and the manner in which these can be used to develop management strategies for the prevention of fragility fracture. As such it aims to stimulate a cohesive approach to the management of osteoporosis in patients with CKD G4-G5D, to replace current variation in care and treatment nihilism. This consensus paper builds on guidance issued for the diagnosis and management of osteoporosis in postmenopausal women[23;24]. Given the paucity of systematic reviews, meta-analyses and randomized controlled trials specifically dealing with the topic of osteoporosis in CKD G4-G5D, mainly original manuscripts have been used to provide the evidence base. In the preparation of this consensus paper, a survey on the topic was sent to members of the Committee of Scientific Advisors (CSA) and the Committee of National Societies (CNS) of the International Osteoporosis Foundation (IOF) and members of the European Renal Association - European Dialysis and Transplant

Association (ERA-EDTA) CKD-MBD working group. Results of the survey were discussed in a face-to-face meeting comprising an expert panel of nephrologists and metabolic bone specialists. This consensus paper was endorsed by the CSA and the CNS of the IOF and by the European Renal Osteodystrophy (EUROD) workgroup[25].

PATHOPHYSIOLOGY OF BONE FRAGILITY IN CKD G4-G5D

A proper understanding of the pathophysiology of bone fragility in the setting of CKD G4-G5D may help to define the optimal diagnostic and therapeutic approach. However, a detailed discussion of this topic is beyond the scope of this consensus paper, and can be found in excellent reviews elsewhere[26;27]. It is important to acknowledge that bone fragility in CKD G4-G5D is the composite of primary osteoporosis, drug-induced and CKD-related bone abnormalities. First, primary age-related and postmenopausal osteoporosis may manifest itself in CKD patients at a younger chronological age, consistent with the notion that in bone as well as other tissues, CKD is a state of accelerated/premature ageing. Second, CKD patients are often treated with a multitude of drugs, many of them having proven or putative detrimental bone effects. Examples include corticosteroids, loop diuretics, heparin, proton pump inhibitors[28], and vitamin K antagonists[29]. Third, the uremic environment, characterized by (micro)inflammation, metabolic acidosis, accumulation of uremic toxins [27;30] and disturbances in calcium, phosphate, parathyroid hormone (PTH) and vitamin D metabolism causes renal bone disease, commonly referred to as renal osteodystrophy (ROD). ROD encompasses abnormalities in bone turnover (remodeling), mineralization and volume, which alone or in combination may impair bone strength. High turnover bone disease, which is essentially the histological expression of secondary hyperparathyroidism (SHPT), has long been the predominant type of ROD, but in the last two decades low turnover bone disease, mostly of the adynamic type, has become increasingly prominent in dialysis patients[31-33]. Mineralization defects have waned over time and are rather uncommon in contemporaneous adult dialysis patients [31-33]. The uremic milieu contributes to alterations of the biochemical composition of bone, including matrix composition,

mineral to matrix ratio and crystallinity, thereby affecting bone quality negatively [30].In addition, systemic diseases that can affect kidney function (e.g. diabetes[34], systemic lupus erythematosus[35]) and primary renal diseases (e.g. autosomal dominant polycystic kidney disease[36]) may be associated with a specific bone phenotype that may predispose to fractures.

Various paracrine and endocrine signals participate in bone remodeling, with the Wnt/β-catenin pathway and PTH playing a central role[37;38]. Direct effects of PTH on osteoblasts and osteocytes, and indirect actions on osteoclasts, promote both bone formation and bone resorption. The final effect on bone mass, either anabolic or catabolic, appears to depend on the duration, intensity and periodicity of PTH exposure. Bone resorption predominates in response to continuous exposure to high circulating PTH levels, whereas intermittent PTH administration leads to a net increase in bone mass. Continuous as compared to intermittent PTH exposure regulates, in bone cells, different sets of genes or, alternatively, affects the same sets of genes in a sustained versus transient manner, the first favoring bone resorption and the second bone formation. PTH receptor type 1 (PTH1R) signaling in osteoblasts and osteocytes can increase the receptor activator of nuclear factor [kappa]-B ligand/osteoprotegerin (RANKL/OPG) ratio. The OPG-RANKL-RANK pathway appears to be the main mediator of the catabolic actions of PTH. Moreover, continuous exposure to PTH causes a sustained upregulation of monocyte chemoattractant protein-1 (MCP-1), another mediator of bone resorption. The anabolic effect of PTH on bone, conversely, seems to be mediated largely through canonical Wnt/β-catenin signaling. PTH may increase Wnt/β-catenin signaling both directly and indirectly, e.g. by repressing the osteocytic expression of secreted Wnt antagonist sclerostin[39]. Conversely, increased expression of Wnt inhibitors can oppose PTH actions in early CKD [38;40]. It is increasingly acknowledged that PTH hyporesponsiveness is as much an integral component of CKD-MBD as elevated circulating PTH levels [41].

Signals to the bone, either mechanical or chemical (including therapeutics), can differentially affect the cortical and trabecular bone compartments [42]. Experimental and clinical evidence indicate that high PTH signaling predominantly causes cortical bone loss through increases in cortical porosity and thinning due to endocortical

trabecularization[43;44].This may also explain why peripheral fractures are especially common in CKD patients.

DIAGNOSIS OF OSTEOPOROSIS IN CKD G4-G5D

Osteoporosis, as described by the World Health Organization (WHO) since 1994, and then by the National Institute of Health (NIH), is a condition characterized by low bone mass and microarchitectural bone deterioration that leads to bone fragility and fracture susceptibility [5]. Its operational definition is based on an areal bone mineral density (BMD) assessed by dual energy X-ray absorptiometry (DXA) at spine or hip ≤-2.5 SD from the sex-matched BMD in young adults. CKD G4-G5D is often considered one of the exclusions for this definition. We stand for an inclusive definition of osteoporosis, including also patients with CKD 4-5D, in spite of the contributions of ROD to the decreased bone strength in this population. Since CKD is a state of accelerated ageing, primary osteoporosis may also play a more prominent role in bone fragility in CKD G4-G5D patients than previously anticipated and may eventually overcome the impact of ROD itself.

RISK FACTORS FOR FRAGILITY FRACTURES RISK IN CKD G4-G5D

Clinical risk factors

Clinical risk factors contribute to fracture risk over and above that provided by BMD. Classic clinical risk factors for fracture include age, sex, low body mass index, parental history of hip fracture, current smoking, alcohol intake of 3 or more units daily and causes of secondary osteoporosis (e.g. type 2 diabetes), and probably most importantly, a previous fragility fracture. These risk factors also apply to patients with CKD G4-G5D [45]. In addition, a long dialysis duration has been identified as risk factor for fracture in CKD G5D patients[16].

Bone Mineral Density

Assessment of BMD has provided a pivotal determinant of fracture risk in the non-CKD population. In general, all densitometric techniques have high specificity but low sensitivity. Dual energy X-ray absorptiometry (DXA) is widely available and is the

clinical standard to measure BMD and fracture risk. DXA does not have sufficient resolution to discriminate between cortical and trabecular bone and between deficits in bone volume or mineralization. Several sources of bias may hamper the interpretation of DXA data at the lumbar spine. These include compression fractures, calcification of the abdominal aorta, orthopedic deformities (scoliosis, hypertrophic degenerative disease, focal sclerotic bone disease), and calcium, barium (or lanthanum) within the gastrointestinal tract. Many cross-sectional and prospective population studies indicate that the risk for fracture increases by a factor of 1.5 to 3.0 for each standard deviation decrease in BMD. The association between BMD and fracture risk is continuous. Hence, given osteopenia is much commoner than osteoporosis, most fragility fractures occur in individuals with osteopenia. Increases in BMD with treatment, furthermore, account for up to 80 % of the fracture risk reduction[46;47], confirming the critical role of reduced BMD as a risk factor for fractures and treatment target in the non-CKD population.

An increasing body of evidence indicates that DXA may predict fractures in CKD as well as in the non-CKD population[10;48-51], although some doubt remains as to the consistency of the fracture risk prediction by DXA across stages of CKD and degree of PTH control[10;48]. Accounting for these data, KDIGO now supports BMD testing in patients with CKD G3a-G5D with evidence of CKD-MBD and/or risk factors for osteoporosis. An important qualifier is that BMD testing should be performed only <u>if results will impact treatment decisions</u> (guideline 3.2.1. 2017 update)[52]. Importantly, since DXA does not inform on bone quality, being commonly impaired in advanced CKD, it most probably underestimates the actual fracture risk in these patients. The implementation of BMD testing in clinical CKD practice raises the following practical questions: who to test, which skeletal site(s) to select, and what time interval to adopt for a repeat testing?

ASSESSMENT OF FRACTURE RISK

Bone mineral density (BMD), as assessed by DXA

The role of BMD measurement for the assessment of fracture risk depends on ease of access to densitometry and overall fracture risk profile, and should not be different in individuals with and without (advanced) CKD. At present, there is no universally

accepted policy for population screening (routine testing) in Europe to identify patients with osteoporosis or those at high risk of fracture. Patients overall are identified opportunistically using a case-finding strategy, on the finding of a previous fragility fracture, or the presence of significant risk factors[23]. With the increasing development of effective agents and price reductions and the improving access to densitometry, the screening policy may change, particularly for populations at high risk, including CKD patients. Reviewing guidelines for the general population, several bone societies recommend BMD screening in females and males above 65 and 70 years, respectively. In younger patients, BMD screening is recommended if either postmenopausal or older than 50 years AND considered high risk[53;54](International Society of Clinical Densitometry, "2015 ISCD official positions—adult," 2015, http://www.iscd.org/official-positions/2015-iscd-official-positions-adult/). Considering CKD patients at high risk, DXA testing in patients with CKD G4-G5D may thus be considered in postmenopausal women and patients aged > 50yrs. This recommendation is opinion based and needs to be confirmed by large scale screening studies. We also acknowledge the difficulty to clinically distinguish menopause from the commonly occurring amenorrhea in premenopausal women with advanced kidney disease.

Which skeletal site(s) to select?

As in the general population, the hip and the lumbar spine are the primary skeletal site to evaluate BMD by DXA in patients with CKD G4-G5D. Since SHPT primarily affects cortical bone, DXA data at cortical rich skeletal sites (e.g. mid shaft radius 90% cortical bone, femoral neck 75% cortical bone) may be hypothesized to allow better fracture discrimination, although clinical studies so far have largely failed to support this hypothesis [10;55;56]. A relatively low prevalence of hyperparathyroid bone disease in contemporaneous patients with CKD G4-G5D[31;32], a high operator variability for forearm (radius) measurements, and bias by a functioning arteriovenous fistula[57;58]may have limited statistical power.

What time interval to adopt for a repeat DXA?

The optimal interval for repeating DXA scans is uncertain, but because changes in bone density over short intervals are often smaller than the measurement error of most DXA scanners, at least in the general population, frequent testing (e.g., < 2 years) is unnecessary in most patients, unless the rate of loss is expected to exceed the least significant change for that DXA machine (i.e. > 2-3%). Even in high-risk patients receiving drug therapy for osteoporosis, DXA changes at the individual level are small compared to measurement error and changes may take over 3 years to be significant[59]. Therefore, DXA should only be repeated if the result will influence clinical management or if rapid changes in bone density are expected. There is a paucity of information regarding long-term changes in (cortical and trabecular) bone mass in patients with CKD G4-G5D. Compared to individuals with normal kidney function, the decline of BMD is accelerated in elderly women with CKD[13;60]. A recent 2-year prospective study in 89 hemodialysis patients reported a 1.2% and 3.1% decline of BMD at the total hip after 1 and 2 years, respectively; BMD at the spine was unchanged during the study period[61].

Vertebral Fracture Assessment

Vertebral fractures are common in patients with CKD, as in the general population[17;62].The majority of vertebral fractures do not come to medical attention and thus remain undiagnosed. Many guidelines for the diagnosis and management of osteoporosis in postmenopausal women emphasize the importance of identifying vertebral fractures and promote more frequent use of vertebral imaging for fracture risk assessment and determining the need for pharmacotherapy [63]. It is reasonable to adopt the International Society for Clinical Densitometry (ISCD) guidelines with regard to vertebral fracture assessment (VFA) in patients with CKD G4-G5D. The ISCD recommends lateral spine imaging with standard radiography or densitometric VFA when T-score is < -1.0 and of one or more of the following is present: (a) Women age ≥ 70 years or men ≥ age 80 years; (b) Historical height loss > 4 cm (>1.5 inches); (c) Self-reported but undocumented prior vertebral fracture; (d) Glucocorticoid therapy equivalent to ≥ 5 mg of prednisone or equivalent per day for ≥ 3 months.

Lateral XR or DXA of the (lumbar) spine also allows assessment of abdominal aortic calcification[64] and thus may be useful in concomitantly stratifying cardiovascular risk[65].

Trabecular bone score and alternative imaging techniques

Trabecular bone score (TBS) is a recently developed analytical tool that performs novel grey-level texture measurements on lumbar spine DXA images, and thereby captures information relating to trabecular microarchitecture. In the general population, TBS has been shown to be a predictor for fracture independent of BMD and clinical risk factors (e.g. FRAX score)[66]. Recent evidence indicates that TBS may also represent a useful adjunct to BMD to discriminate fracture status (non-vertebral fractures) in the dialysis population[67] and to predict fractures in patients with mild renal impairment and after kidney transplantation [68]. TBS as well as other DXA-based bone texture measurements, however, need further clinical evaluation before considering their implementation in clinical practice can be advocated.

Alternative imaging techniques, able to distinguish between cortical and trabecular bone such as (HR-)pQCT and MRI, have been postulated to prove superior to DXA in discriminating fractures in CKD, but so far yielded conflicting results [43;69-72]. QCT may be more sensitive than DXA for monitoring bone loss at the hip in CKD[61].

Falls risk

Falls history is an independent risk factor for fracture in the general population[73]. Also in CKD patients, a history of falls associates with fractures[74]. Falls risk should be taken into consideration when assessing whether or not to commence medication for osteoporosis and should also alert the physician to the opportunity to target falls risk directly (see below). According to a secondary analysis of data collected in the 2014 Behavioral Risk Factor Surveillance System, adults aged 65 or older with CKD are at increased risk of falling and of suffering an injury as a result of a fall compared with adults in the same age range without CKD [75]. Also, dialysis patients have a higher falls risk than non-CKD counterparts [76-78]. Key to minimizing falls risk is an evaluation of secondary causes - including (orthostatic) hypotension, bradycardia, psychotropic

drugs, sarcopenia and neuropathy, and decreased vision. Various simple questionnaires allow estimates of falls risk to be made. Poor performance on tests of neuromuscular function (including timed up-and-go and 6-min walk tests) also may identify those at higher risk of fracture in CKD[74]. This is likely to reflect their higher risk of falls due to impaired muscle strength.

Fracture risk assessment tools

The limitations of DXA BMD for risk assessment have stimulated the development of risk prediction algorithms that integrate several risk factors for fracture. These include the Garvan fracture risk calculator, QFracture® and FRAX®. Of these, FRAX® (https://www.sheffield.ac.uk/FRAX/tool.aspx) has been the most extensively used[23]. FRAX® is a computer-based algorithm that calculates the 10-year probability of a major fracture (hip, clinical spine, humerus or wrist fracture) and 10-year probability of hip fracture. A unique feature of FRAX® is that it considers competing mortality in the fracture risk estimation procedure. The various FRAX® tools have been refined in different countries to take into account the genetics of bone fracture. There are many risk factors for fractures used in FRAX®, including age, sex, body mass index, family history, alcohol use, smoking, glucocorticoids, and rheumatoid arthritis. There is also an option to say yes or no to secondary osteoporosis, including diabetes, osteogenesis imperfecta, long-standing hyperthyroidism, hypogonadism, premature menopause, chronic malnutrition, or malabsorption and chronic liver disease. The addition of BMD to the FRAX® score improves the prediction of fracture risk. FRAX® is an easy and well-validated tool, but also has some limitations, e.g. it does not account for dose-responses for several risk factors does not account for the time dependency of several key risk factors or incorporate falls risk. *Noticeably absent in the list of secondary causes of osteoporosis is the presence of CKD.* Despite this limitation, mounting evidence confirms that FRAX® performs as well in patients with CKD as in the general population for fracture discrimination and fracture risk prediction[50;76;79;80]. Intuitively, one would expect that FRAX underestimates fracture risk in CKD as it does in diabetes mellitus. However, both under- and overestimation of the absolute fracture risk has

been reported[50;80]. As previously mentioned, the FRAX® risk engine considers competing mortality in the fracture risk estimation procedure. CKD patients not only have an increased fracture risk but also have a limited life expectancy. The impact of CKD on the FRAX® score thus may prove to be neutral. Additional large epidemiological studies are required to define whether further arithmetic adjustments to conventional FRAX estimates have to be made with knowledge of CKD G4-G5D. At least in the general population, FRAX with BMD can identify fractures better than FRAX alone[81].

Bone turnover markers

In the general population, bone-specific alkaline phosphatase (BALP), procollagen type I N propeptide (PINP) and C-terminal cross-linking telopeptide of type I collagen (CTX) associate with future risk of fractures, although only modestly at best[82-84]; however, the ability for CTX and PINP to predict incident hip fractures in postmenopausal women has recently been challenged[85].The association of bone turnover markers (BTMs) with fracture risk in individuals with CKD is even less clear. To avoid bias related to renal retention, BTMs that are not cleared by the kidneys, such as BALP, trimeric PINP, and tartrate-resistant acid phosphatase-5b (TRAP-5b), should be considered in the setting of CKD. Total alkaline phosphatase, which is routinely monitored in CKD patients, is a valid surrogate for BALP in the absence of liver dysfunction. Epidemiological data suggest a simple, linear relationship between total alkaline phosphatase levels and fracture risk in CKD patients[86]. In hemodialysis patients, BALP outperformed DXA and PTH for the prediction of fracture incidence [48]. After kidney transplantation the association of BALP, PINP, and TRAP5b with fracture risk, conversely, is less clear[10]. Studies investigating the association between PTH and fracture risk show a complex J- or U-shaped relationship, with both very high and very low PTH levels conferring an increased fracture risk[16;87;88]. This observation aligns with clinical and experimental data indicating that both low and high PTH levels with the corresponding low or high bone turnover may impair bone quality [14].

INTERVENTION THRESHOLDS FOR PHARMACOLOGICAL THERAPY

BMD, as assessed by DXA

Whereas BMD provides the cornerstone for the diagnosis of osteoporosis, the use of a fixed BMD cutoff is less than optimal as an intervention threshold. Fracture probability may indeed differ according to country of origin (genetics?) and age category[23]. A T-score ≤ -2.5 at the hip or lumbar spine has been used as an inclusion criterion in most registration studies evaluating anti-osteoporotic drugs for postmenopausal osteoporosis and is widely adopted as intervention threshold in osteoporosis literature. It should be acknowledged that the choice for this intervention threshold is purely arbitrary. Intervention thresholds have ranged from T-scores of − 3.0 to − 1.5 depending on the clinical context, the country or on health economic factors. In diabetics, the intervention threshold has been set a -2.0, accounting for the fact that fracture risk at -2.0 in diabetes is similar to risk at -2.5 in non-diabetes[89]. Comparable data for CKD patients are unfortunately lacking. Therefore, a T-score intervention threshold ≤ -2.5 at the lumbar spine or hip is recommended, recognizing a higher threshold of -2.0 or -1.5 may be more appropriate.

Fracture risk, as assessed by FRAX

Awaiting the results of additional large epidemiological studies defining whether arithmetic adjustments to conventional FRAX estimates have to be made with knowledge of CKD G4-G5D, conventional country specific intervention thresholds as defined for postmenopausal women, may be used as rough guides for patients with CKD G4-G5D[23]. The intervention threshold is most commonly set at the age-specific fracture probability equivalent to individuals with a prior fragility fracture and therefore rises with age. In other words, the intervention threshold is set at the 'fracture threshold'. The thresholds used have varied since they depend critically on local factors such as reimbursement issues, health economic assessment, and willingness to pay for health care in osteoporosis and access to DXA.

History of fragility fracture

As previously emphasized, fragility fractures of the long bones (arms, legs), spine, and pelvis are associated with increased risk of future fractures[19;90], especially in the 12 months following the event[91]. Individuals aged > 50 yrs with a history of such a fragility

fracture may be considered for intervention without the necessity for a BMD test (other than to monitor treatment).

MANAGEMENT

The management of osteoporosis in patients with CKD G1-G3 is as for the general population, as long as there are no biochemical abnormalities suggesting the presence of CKD-MBD. Clinicians dealing with such patients are referred to guidance and guidelines as issued by several bone and endocrine societies[23]. The management of osteoporosis in patients with CKD stages G4-G5D is more of a challenge. Concerns with regard to efficacy and safety of available non-pharmacological and pharmacological approaches in the setting of CKD G4-G5D cause hesitancy and inertia among clinicians. A recent systemic review, updating evidence on the efficacy and safety of common osteoporosis medications (including bisphosphonates, teriparatide, raloxifene, and denosumab) among CKD patients concluded that effects on BMD, fracture risk, and safety are not clearly established[20]. That said, absence of evidence does not equate to evidence of an absence of effect. Many large registration trials of new osteoporosis drugs excluded patients with overt renal failure (CKD G4-G5D), mainly for 2 reasons: renal safety concerns and unpredictable bias by ROD. This consensus paper aims to provide some guidance on the management of osteoporosis in patients with advanced CKD, awaiting further high quality data [92]. Reflecting the complex pathophysiology, therapy of osteoporosis in CKD G4-G5D should be multifaceted and include control of CKD-MBD, control of uremia and specific osteoporosis management.

Control of CKD-MBD

A first step in controlling the fracture risk in CKD G4-G5D patients is optimizing CKD-MBD treatment. A detailed discussion of the optimal treatment of CKD-MBD is beyond the scope of this position paper and can be found in recent guidelines and review papers[52]. We herein briefly elaborate on the role of a bone biopsy and bone turnover markers in the work-up of a patient with osteoporosis and advanced CKD.

Histomorphometric analysis of a tetracycline double-labeled iliac crest bone biopsy remains the golden standard for the diagnosis of disturbances of bone turnover and mineralization in CKD, both of which may affect bone strength independent of bone mass. Bone biopsies are underused by clinicians, largely because of the invasive character of the procedure, but also because worldwide only few centres are able to perform histologic and histomorphometric analyses of bone biopsies and progressively are vanishing. Current procedures using Yamshidi-type needles with inner diameter < 4 mm, local anaesthesia and light sedation (midazolam) are better tolerated, and can easily be performed in an outpatient setting[25]. Further, there is considerable variability between biopsies taken from different sites and the same time in the same patient[93].

Several circulating biomarkers have been suggested for the clinical differentiation between high and low bone turnover in CKD, the most well established being PTH and BALP (see above). The quest for the optimal bone turnover marker (panel) is ongoing but so far, no single biomarker or combination of biomarkers has approached the diagnostic accuracy of a bone biopsy[94]. The association of fibroblast growth factor 23 (FGF23), sclerostin, and circulating miRNA signatures with bone health in patients with CKD remains a topic of ongoing research[95-97]. Individual treatment decisions should be based on trends of BTMs rather than on single time point levels[52].

Importantly, although a bone biopsy may still be relevant in the work-up, KDIGO emphasizes that the inability to perform a bone biopsy may not justify withholding osteoporosis therapy from patients with high risk of fracture[52].

Control of uremia

Efforts should be made to correct metabolic acidosis[98], to avoid chronic mild hyponatremia[99], to reduce CKD- and age-related inflammation[100] and to clear uremic toxins with proven or putative skeletal toxicity[27;30].

Non-pharmacological osteoporosis management

Mobility and falls

Immobilization causes bone loss. Immobilized patients may lose as much bone in a week as they would otherwise lose in a year. Weight-bearing exercise forms an integral component of osteoporosis management. This may be highly relevant in hemodialysis patients, as these patients commonly show a poor and rapidly deteriorating physical performance. Studies investigating the relationship between physical activity and BMD in hemodialysis are few, and, so far, were negative[28]. Exercises to improve muscle strength and balance may reduce the likelihood of falls and may prove effective in reducing fracture rates.

Nutrition

Adequate dietary intakes of key bone nutrients, such as calcium and vitamin D, contribute to bone health and reduce the risk of osteoporosis and of fracture. The Recommended Nutrient Intakes (RNI) are 1000–1200 mg of calcium and 600-800 IU of vitamin D per day in men and women over the age of 50 years[101 102]. The validity of these figures in CKD G4-G5D patients is unclear, given the complexity of calcium homeostasis in this specific setting.

Data from small cohort studies indicate that dietary calcium intake falls below RNI in a substantial proportion of CKD patients, both in the USA[103;104] and Europe [28;105]. Regional variability may be anticipated, reflecting dietary heterogeneity[106;107]. In general, CKD patients free of calcium supplements, should be considered at risk for a negative calcium balance[103;108], which in turn may be a neglected culprit of a low bone mass [28;109]. It is recommended to estimate calcium intake in CKD patients at risk for osteoporosis and fracture (e.g. using user-friendly online calculators) and to adjust dietary intake and/or calcium supplements accordingly. Acknowledging potential cardiovascular risks, otal exogenous elemental calcium supply should not exceed 1200 mg per day. In patients on dialysis, dialysate calcium transfers from the dialysate should additionally be accounted for when estimating dietary calcium needs[108].

Acknowledging that patients with CKD G4-G5D are often vitamin D depleted, KDIGO recommends monitoring 25(OH)D (calcidiol) levels and correcting vitamin D insufficiency and deficiency using treatment regimens with nutritional vitamin D recommended for the general population[110]. The optimal supplementation regimen remains to be defined but the goal should at least be the same as for non CKD patients, namely an optimal 25(OH)D level of 20-30ng/ml (50-75 nmol/L) [102]. Large intermittent doses of nutritional vitamin D should be avoided as this regimen has been associated with an increased risk of fractures and falls.

Vitamin K deficiency is common among patients with CKD G4-G5D[29;111]. Mounting epidemiological evidence shows an association between vitamin K status and fracture risk in patients with CKD G4-G5D[29;112]. It is however too premature to support the routine monitoring of vitamin K status or supplementation with vitamin K in these patients.

Lifestyle modifications

Evidence is limited, but multimodal exercise programs, moderation of alcohol consumption and cessation of smoking have been associated with improved bone health in the general population[113] and therefore their implementation should also be considered in patients with CKD G4-G5D.

Pharmacological osteoporosis management

The most commonly used osteoporosis drugs in Europe are bisphosphonates, denosumab, and agents derived from parathyroid hormone. Recently, also romososumab has been approved for the treatment of osteoporosis. They have all been shown to reduce the risk of vertebral and non-vertebral fracture in postmenopausal women and, in some cases, agents have been shown specifically to decrease fracture risk at the hip. In studies of men, most outcome measures have included BMD and BTMs as surrogates for efficacy, with no fracture endpoints[114].

Fracture prevention trials for these osteoporotic treatment agents included some patients with creatinine in the normal laboratory range but with decreased kidney function, determined by eGFR. Registration studies thus enabled evaluation of the

efficacy and safety of common osteoporosis medication in (female) patients with impaired kidney function as low as CKD G4. It is important to note that all these studies were post-hoc analyses of otherwise healthy individuals with no significant aberrations in markers of mineral metabolism and that follow-up time was rather short (at most 3 years). Treatment recommendations in this consensus paper (***Table 2***) are focused on postmenopausal women and men > 50 years. Evaluation and treatment of younger patients with advanced CKD at increased fracture risk is complex and should be individualized.

Bisphosphonates

Mode of action. Bisphosphonates are stable analogues of the inorganic compound pyrophosphate. They have a strong affinity for bone apatite, both in vitro and in vivo, which is the basis for their clinical use. Bisphosphonates are potent inhibitors of bone resorption and produce their effect by reducing the recruitment and activity of osteoclasts. Potency and mechanism of action varies depending on the length and structure of the side chain. The nitrogen-containing bisphosphonates alendronate, ibandronate, risedronate and zoledronic acid are currently most commonly used [115;116].

Pharmacokinetics and -dynamics. Oral bioavailability of bisphosphonates is low, around 1% of the dose ingested, and is impaired by food, calcium, iron, coffee, tea, and orange juice. Bisphosphonates are not metabolized. Between 27% and 62% of the drug binds to bone mineral and the rest is excreted via the kidneys, predominantly within hours after administration. Of note, the concentration of bisphosphonates is lower in cortical than trabecular bone[116]. The role of bone turnover on skeletal accumulation of bisphosphonates remains unclear; recent preclinical data challenge the hypotheses that skeletal accumulation is increased in high bone turnover states [117].
Bisphosphonates persist in bone for a long time, are slowly released during cycles of bone remodeling, and can reenter the systemic circulation, and also the kidney, with no change observed in their molecular structure or metabolic activity. Renal excretion occurs by both passive glomerular filtration and active transport in renal proximal tubular cells. Experimental and clinical evidence shows increased serum half-life and renal accumulation in the setting of CKD[118]. Bisphosphonates are cleared by dialysis[119].

The efficacy of dialytic clearance varies between bisphosphonates, probably owing to variable protein-binding. Alternative dosing regimens in CKD (lower dose, lower frequency), though theoretically logical, have so far not been validated using clinical endpoints.

Efficacy. Post-hoc analyses of pivotal clinical trials evaluating bisphosphonates found that these drugs had similar efficacy, improved BMD and reduced fractures, in subjects with mild or moderately reduced eGFR (up to CKD G4) compared to those with normal eGFR[120-122]. Studies investigating the efficacy of bisphosphonates in patients with CKD G5, including those on dialysis, or in patients with earlier stage CKD presenting with biochemical disturbances of mineral metabolism are scarce and limited by small sample size and yielded inconsistent findings [123-127]. Patients with high bone turnover at baseline may be anticipated to show the highest BMD gains[128].

Safety. Bisphosphonates have been suggested to compromise skeletal, vascular and renal health. These risks call for caution but needs some nuance.

Suppression of bone turnover is inherent to bisphosphonates and most osteoporosis patients who are treated with bisphosphonates develop a low bone formation rate. There is however no evidence that the level of remodeling suppression in CKD is more than that in non-CKD counterparts [129]. Implications of drug-induced suppression of bone turnover towards bone strength are intensely debated. Decreased bone resorption and formation leads to more secondary mineralization in the bone, so that the bone becomes harder. This may contribute to improving bone strength and reduced fracture risk[130]. Bone remodeling suppression, on the other hand, may also increase collagen crosslinking by advanced glycation end products and thus impair bone quality. Furthermore, according to a recent bone biopsy study, 'over-mineralization' (often referred to as brittle bone) may impair toughening mechanisms in cortical bone, which in turn may confer an increased risk of atypical fractures[131]. Data from a 2015 study of alendronate in postmenopausal women, conversely, suggest that even prolonged reduction in bone turnover is unlikely to be associated with adverse effects on bone material properties[132]. In CKD patients, low PTH levels, as a proxy of low bone turnover, have been associated with increased fracture risk [87;133].

These findings remain to be confirmed by formal bone biopsy studies. Furthermore, it remains a matter of debate whether low bone turnover *per se* or the disease causing low bone turnover disease is accountable for the perceived increased fracture risk. Of note, the 2017 KIDGO update no longer considers a bone biopsy mandatory prior to initiating bisphosphonate therapy[52].

Theoretically, bisphosphonates may both accelerate and attenuate vascular calcification. On the one hand, bisphosphonates reduce bone formation and thereby reduce the ability of bone to buffer exogenous calcium influx. A decreased buffering capacity may increase the risk of transient hypercalcemia and as such promote vascular calcification. In postmenopausal women treated with antiresorptive therapy, however, accelerated vascular calcification has not been reported[134]. On the other hand, bisphosphonates may be hypothezised to suppress vascular calcification. The mechanism may be multifactorial. First, bisphosphonates are analogs of pyrophosphate, which is a potent vascular calcification inhibitor. However, at least in patients with good renal function, conventional doses of nitrogen-containing bisphosphonates fail to yield circulating concentrations that are sufficient to exert direct anti-calcifying effects. Second, by reducing bone turnover, bisphosphonates reduce the bone efflux of phosphate and calcium. In clinical studies, the first generation etidronate markedly reduced progression of vascular calcification in CKD patients[135], while recent generation nitrogen–containing bisphosphonates (alendronate, ibandronate) yielded inconsistent vascular outcomes[124;126;134].

Bisphosphonates have historically been associated with a risk of acute kidney injury (acute tubular necrosis, focal segmental glomerulosclerosis). According to a 2003 review, however, these agents can be administered to patients with various degrees of renal impairment, with no long-term decline in renal function, if used with care and in accordance with the prescribing information. This applies to both oral and IV bisphosphonates. Nevertheless, the low incidence of renal adverse events has led to the inclusion of “warnings” on the prescribing information of all bisphosphonates regarding the use of these agents in patients with severe renal impairment (CrCl<30 or <35 mL/min). For IV zoledronic acid, this warning constitutes a “contraindication” in the registration labels for patients with eGFR<35 mL/min[136]. Renal risks should be

considered when defining the individual risk-benefit ratio in patients with osteoporosis and CKD, even in patients with CKD G5D, as long as there is residual renal function. There is no need for supplementary renal function testing following the initiation of bisphosphonates in patients with CKD G4-G5D.

Other safety concerns with bisphosphonates include an acute phase reaction (IV bisphosphonates only), oesophagitis, atrial fibrillation, hypocalcemia, osteonecrosis of the jaw (ONJ) and atypical subtrochanteric fractures. The incidence of ONJ and atypical fractures in the osteoporosis patient population is very low and is estimated at 1-90 and 7-9 per 100000 patients years of exposure, respectively[137-139]. Otherwise stated, for each atypical femur fracture, >1200 fractures, including 135 hip fractures, are prevented[137]. For ONJ and atypical subtrochanteric fractures, the risk is reported to be higher with a longer duration of bisphosphonate therapy. Pre-existing dental disease and prior dental extraction are the highest risk factors for ONJ. Any dental disease which requires intervention and poor oral hygiene should be addressed prior to proceeding with antiresorptive therapy [138;139].

In aggregate, efficacy and safety of bisphosphonates in patients with CKD G4-G5D needs further clarification. At present, there is however no clear reason to assume that the overall risk-benefit ratio of therapy with bisphosphonates is less favorable in patients with CKD G4-G5D than in the general population. When considering off-label use, patients should be properly informed about potential risks, benefits, and alternatives and notes should be taken in the patients' file [140]. Whether a different dosing regimen is required and whether duration of therapy should be shorter in patients with CKD G4-G5D, remains to be investigated. Awaiting this evidence, classical dosing regimens may be used in patients with CKD G4-G5D, although regimens using lower doses or longer intervals may be equally valid. In patients without residual renal function (no renal risks), intravenous formulations may be preferred in order to limit pill burden, to avoid interference with phosphate binders (lower bioavailability) and to exclude non-adherence. As in the general population, it is reasonable to reassess CKD patients after 3 years of therapy or after a new fracture using FRAX® with femoral neck BMD.

Denosumab

Mode of action. Denosumab is a fully human monoclonal antibody against receptor activator of nuclear factor kappa ligand (RANKL), a cytokine that is essential for the formation, function, and survival of osteoclasts. By binding RANKL, denosumab prevents the interaction of RANKL with its receptor, RANK, on osteoclasts and osteoclasts precursors and reversibly inhibits osteoclast-mediated bone resorption[115;116].

Pharmacokinetics and –dynamics. At variance with bisphosphonates, renal function does not have a significant effect on denosumab pharmacokinetics and -dynamics[141].

Efficacy. Every six month administration of intravenous denosumab has been shown to improve BMD in CKD G4-G5D in a post-hoc analysis of the large Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months (FREEDOM) registration trial[142] and in small open label pilot studies[126;143;144]. As for bisphosphonates, it can be speculated BMD gain will be less in patients with low bone turnover at baseline, although there is no hard evidence to support this view. Animal data indicate that denosumab may impact on bone not only by suppressing bone resorption, but also by maintaining, perhaps slightly stimulating (periosteal) modeling-based bone formation [145]. The contribution of periosteal modeling-based bone formation to the overall BMD gains in denosumab treated patients remains to be defined. Periosteal modeling-based bone formation may also explain why steady BMD gains are observed during prolonged remodeling inhibition in the general population [146]. Periosteal modeling-based bone formation may also have contributed to the up to 5% increase in lumbar spine bone mass has been reported in denosumab treated *de novo* renal transplant recipients[147], many of them may have had low-normal bone turnover at baseline.

Safety. A major concern with the use of denosumab in CKD is the increased risk of severe and symptomatic hypocalcemia. The risk of denosumab-induced hypocalcemia seems to be highest in patients with increased bone turnover at baseline. According to a recent meta-analysis, calcium levels reach a nadir in the first 2 weeks up to 2 months after dosing[143]. This complication resembles the hungry bone syndrome, observed following potent PTH suppression therapy [148]. Hypocalcemia can be alleviated by

preemptive calcium and vitamin D supplementation and using a high-calcium bath in dialysed subjects[143;149].

Another major concern is the offset of effect. While bisphosphonates are retained by the skeleton and treatment cessation is associated with slow bone release, for denosumab the bone loss is rapid. All the bone gain on therapy at the hip is lost within 6 months and associated with a 30% increase in vertebral fractures (4.2 vs.3.2%)[150]. Hence denosumab should either be administered continuously or followed by some alternative antiresorptive therapy. Bone turnover markers may be useful to monitor the offset of effect in patients (see below)[151].

From a nephrological perspective, similar concerns as for bisphosphonates exist for denosumab with regard to potential implications of a decreased bone turnover on bone strength. As previously mentioned, steady BMD gains are observed during prolonged remodeling inhibition with denosumab in the general population, while bone strength is preserved [146]. It needs to be re-emphasized that (iatrogenic) low bone turnover does not equal low bone turnover disease/adynamic bone disease. The mechanisms contributing to the latter, rather than the low bone turnover *per se* may underlie the association of low bone turnover disease/adynamic bone disease with poor outcomes. An association between low bone turnover disease/adynamic bone disease (as determined by histomorphometry) and incident fractures remains to be demonstrated.

Whereas in the bone compartment the role of RANKL and OPG is well defined, in the vascular compartment, the exact role of RANKL and OPG is more controversial, with preclinical findings[152] being not consistent with human epidemiological observations[153;154]. It is reassuring that in a post hoc analysis of the FREEDOM trial, frequency of aortic calcification (AC) progression over 3 years did not differ between postmenopausal women in placebo (22%) and denosumab (22%) groups ($p = 0.98$). Of note, AC progression did not differ between treatment groups when analyzed by baseline estimated glomerular filtration rate or by baseline AC scores[155]. Along with these findings, therapy with either alendronate or denosumab up to 1 year did not

affect indices of vascular health indices (including vascular calcification scores) in dialysis patients[126 156].

As with bisphosphonates, denosumab therapy associates with ONJ and atypical fractures, but absolute risks are very low [138]. Whereas bone turnover is permanently suppressed for the duration of bisphosphonate therapy and even thereafter (long skeletal $t_{1/2}$), bone turnover in denosumab treated patients shows an early profound drop and thereafter partly recovers up to the next administration. Whether these differences in pharmacodynamics translate in different risks of atypical fractures remains to be seen.

Evidence from recent trials suggests the risk of new clinical fractures, and vertebral fracture increases when osteoporosis treatment with bisphosphonates or denosumab is stopped. These data question the view that patients on long-term treatment with bisphosphonates or denosumab should always be offered a drug holiday. Different pharmacokinetic properties for different therapies and target populations require different strategies to manage drug intermission [139].

Finally, it is important to note that antiresorptive agents do not impair fracture healing.

PTH analogues

Mode of action. Teriparatide (PTH1–34) is a recombinant peptide consisting of the first 34 amino acids of human PTH. Teriparatide regulates both bone formation and resorption, whereby intermittent exposure results in a restoration of bone microarchitecture through an increase in the number and thickness of trabeculae and accelerated mineralization. It may also increase cortical thickness, mainly by endocortical apposition, however cortical bone density decreases due to intracortical remodeling and an increase in cortical porosity. Abaloparatide is an analog of PTH-related peptide designed to have relatively greater affinity for the transient state of PTHR1 receptor, thus potentially being more anabolic[116].

Pharmacokinetics and -dynamics. Giving PTH to patients with CKD–MBD, in whom hyperparathyroidism is a prominent feature, seems counterintuitive. A high circulating

PTH levels however does not equal high PTH signaling. PTH hyporesponsiveness or resistance is a major issue in CKD G4-G5D[41] and may explain why bone turnover is low-normal in the majority of dialysis patients, despite these patients presenting with high PTH levels (well within the KDIGO target)[31;32]. Intermittent PTH boluses in patients with absolute or relative hypoparathyroidism may be hypothesized to elicit an anabolic bone response and improve bone strength. The impact of CKD on the pharmacokinetics and -dynamics of PTH analogs remains to be investigated. Recent animal data suggest that that intermittent teriparatide therapy may elicit an anabolic response in bone even in the presence of secondary hyperparathyroidism[157].

Efficacy. Data proving the efficacy of teriparatide in CKD are scarce. One double-blind trial of 1,637 ambulatory postmenopausal women treated with teriparatide found that reductions in the risk of vertebral and nonvertebral fractures, as well as treatment-emergent and renal-related adverse events, were similar among patients with mild to moderate renal impairment and those without renal impairment[158]. A post-hoc analysis of a post-marketing study in Japan also showed promising results in female patients with CKD G4-G5D not yet on dialysis [159]. Pilot studies in dialysis patients focused on patients with hypoparathyroidism[160] or proven adynamic bone disease [123;161]. In these patients, teriparatide increased (lumbar spine) BMD and biomarkers of bone formation. Taken together, teriparatide may be valid option in patients with CKD G4-G5D in whom high bone turnover has been excluded. The optimal dosing regimen (dose, frequency) remains to be determined. Patients with irreversible adynamic bone disease (e.g. due to post parathyroidectomy hypoparathyroidism) may be best suited for teriparatide therapy. Experimental and clinical evidence demonstrated the ability of abaloparatide to increase bone mass and formation with less risk of hypercalcemia. Data in patients with CKD-MBD are lacking so far.

Safety. Transient hypotension has been reported in 36% of hemodialysis treated with once weekly teriparatide[160]. Because of the long-term risk of osteosarcoma in preclinical models, duration of therapy with PTH should not exceed 2 years.

<u>Romosozumab</u>

Mode of action. Romosozumab is a fully human monoclonal antibody against sclerostin. Sclerostin is a glycoprotein almost exclusively secreted by osteocytes. It inhibits Wnt signaling, which is a key negative regulator of bone formation[37;116]. Since inhibition of sclerostin favors bone formation over resorption, it could provide great utility in treating osteoporosis in patients with CKD G4-G5D, given the high prevalence of low bone turnover in this patient population. Of note, anti-sclerostin antibody treatment on animals with advanced CKD improve bone properties only when the PTH levels were low[162]. These data raise the hypothesis that anti-sclerostin antibodies might not work in presence of high PTH. This hypothesis however conflicts with other experimental studies showing synergistic effects of PTH analogues and sclerostin antibodies[163].

Pharmacokinetics and -dynamics. Data on the impact of CKD G4-G5D on the pharmacokinetics and –dynamics of romosozumab are limited. Following a 210 mg dose of romosozumab in a clinical study of 16 patients with CKD G4-G5D, mean Cmax and AUC were 29% and 44% higher respectively in patients with severe renal impairment compared to those in healthy subjects; romosozumab exposure was similar between patients with ESRD requiring hemodialysis and healthy subjects (UCB data on file. 2.7.2 Romosozumab Summary of Clinical Pharmacology Studies; Section 3.3. Subjects with renal impairment; p83)

Population pharmacokinetic analysis indicated an increase in romosozumab exposure with increasing severity of renal impairment. However, as the exposure in severely impaired renal function is below that of tolerated clinical doses, this increase is not considered clinically meaningful and no dose adjustment is necessary in these patients.

Efficacy. In clinical trials, romosozumab resulted in an increase in BMD to a greater extent than alendronate and teriparatide and a decrease in risk of vertebral and nonvertebral fractures in postmenopausal women[164-166]. Romosozumab also increased the spine and hip BMD compared with placebo in men with osteoporosis [114]. Furthermore, of high interest to patients with CKD, which is associated with cortical losses from the actions of PTH, Langdahl *et al.* reported that cortical BMD increased in greater proportion to trabecular BMD over 12 months in patients switched from a

bisphosphonate to romosozumab[167]. Moreover, the comparator group, in which subjects were switched to teriparatide, experienced a decrease in cortical BMD. It is interesting to note that the bone turnover marker data from these trials suggested an uncoupling of bone remodeling in favor of bone formation, which might be an advantageous pharmacologic property for patients with CKD. For example, bone formation markers increased within a week of administration of romosozumab and peaked at 14 days to 1 month before declining toward or below baseline levels, whereas bone resorption markers decreased from baseline within a week of administration and remained below baseline for at least 12 months[164-166]. Recent follow-up data indicate that the sequence of romosozumab followed by denosumab may be a promising regimen for the treatment of osteoporosis[168]. On April 9, 2019, the FDA approved romomozumab for the treatment of postmenopausal women, with no eGFR cut-off. Data on the efficacy of romomozumab in CKD patients, so far, are lacking. Similar to denosumab, a bone turnover rebound and rapid bone loss has been observed post romosozumab. Hence, patients who discontinue romosozumab should rapidly transition to an antiresorptive treatment.

Safety. Some of the large registration trials raised some concerns with regard to the cardiovascular safety of romosozumab. Saag *et al.* showed an increase in serious cardiovascular adverse events (odds ratio [OR], 1.31; 95% confidence interval [95% CI], 0.85 to 2.00) in postmenopausal women with osteoporosis given 12 months of romosozumab followed by 12 months of alendronate versus 24 continuous months of alendronate [165]. It is important to note that cardiovascular events have not been reported in other studies[166;167]. Whether these results indicate that romosozumab increases cardiac risk or that alendronate is cardioprotective is not known. In a recent phase III randomized placebo-controlled double-blind study in men with osteoporosis, Liewicki *et al.* also noted a high number of adjudicated cardiovascular serious adverse events in romosozumab treated patients (4.9% vs placebo 2.5%). Sclerostin is constitutively expressed in the arterial vasculature and upregulated in foci of vascular calcification. Similar findings have been shown in experimental models with other Wnt inhibitors such as dickkopf-related protein 1 (DKK1) and secreted frizzled related protein (Srfp)[38]. Vascular sclerostin may provide a pathophysiological clue to the

putative increased cardiovascular risk in romosuzumab treated individuals. Experimental and clinical data suggest that sclerostin may act as a paracrine calcification inhibitor, similar to as OPG[169;170]. Additional experimental and clinical studies are required to investigate the vascular role of sclerostin and to define whether systemic blocking of sclerostin confers cardiovascular risks, and if so, whether this is condition-dependent[171].

MONITORING

Adherence

Non-adherence to medical therapy is a widespread public health problem, and especially common in patients with CKD including those on dialysis. Several patient-related, disease-related, and treatment-related factors can contribute to non-adherence in CKD patients[172]. In general, overcoming non-adherence presents particular challenges in asymptomatic bone diseases and other chronic, asymptomatic conditions. One-year compliance is 50–70% for antihypertensives and 25–40% for statins. Similarly, compliance is poor with osteoporosis therapies, ranging from less than 25% to around 75% at 1 year, with mean persistence around 245 days[173]. In such settings, the level of perceived threat to health does not motivate the patient to adhere to therapy. In addition, risk of non-adherence with any therapy increases with increased duration of treatment. Poor adherence to medication is associated with adverse effects on outcomes. Patients' belief in a medication contributes to better adherence, emphasizing the important role of patient education and counseling.

Methods of monitoring of treatment

The different methods of monitoring response to anti-osteoporosis medication include patient reported outcomes, clinician interview, patient questionnaire, bone turnover markers, bone mineral density and other imaging modalities.

<u>BMD, as assessed by DXA</u>

Treatment periods ≥ 3 years are necessary to show a measurable and reproducible BMD response to oral bisphosphonate therapy in postmenopausal women[59]. Early monitoring of BMD thus has limited value in the prediction of treatment responses, at least with inhibitors of bone resorption, and as such is of little value to give biofeedback[23]. On the other hand, analyses of randomized placebo-controlled trials of approved agents to treat osteoporosis have generally shown that larger increases in BMD are associated with greater reduction in fracture risk, at least in postmenopausal women. The paradigm of treat-to-target is aimed at enhancing and individualizing the care of patients with osteoporosis. Based on the best available data, the most promising target is T-score > -2.5. More data are needed to see whether this target is relevant in CKD.

Bone turnover markers

Treatment-induced changes in BTMs are more rapid and do inform on BMD changes, also in the setting of CKD[174]. Absence of suppression of bone turnover markers 3–6 months or so after starting anti-resorptive treatment should trigger the reassessment of adherence to the treatment and also other potential issues with the drug (e.g. improper drug administration)[23;175]. Given the high biological variability of BTMs, least significant changes (LSC) should be considered when evaluating the treatment response. Biofeedback by BTMs only results in a beneficial response to treatment [173] in those demonstrating a positive response. The measurement of BTMs after withdrawal of osteoporosis therapy is potentially also useful to evaluate patients that are taking a pause from treatment. An increase in BTMs more than the LSC reflects loss of treatment effect and identifies patients that are likely to have a decrease in BMD. Such changes could provide an indication for reintroduction of treatment[151]. As previously mentioned, non-kidney-retained bone turnover markers (BALP, trimeric P1NP, TRAP5b), are preferentially used in the setting of CKD, especially in patients with non-stable kidney function[94]. Further, PINP and CTX are significantly and variably increased after a fragility fracture from 2 to 365, limiting their use in the post fracture setting [84].

FRACTURE LIAISON SERVICES

The risk of subsequent fracture is time-dependent, with much higher fracture risk in the first 2 years after an index fracture. This so-called “imminent fracture risk” requires rapid treatment initiation with agents with a short time to onset [176]. Since the majority of patients presenting with fragility fracture do not receive appropriate assessment and treatment, fracture liaison services (FLS) address this need through a systematic approach to identify cases, assess risk of further fractures (including falls risk) and the need for treatment[177]. A nephrologist should be part of the multidisciplinary team to guarantee optimal osteoporosis care to patients with CKD G4-5D. The benefits of FLS to ensure appropriate management of patients without advanced CKD following a fracture are well established: improved adherence to osteoporosis drugs with an expected reduction of the incident fracture rate and decreased post-fracture mortality [23;178].

RESEARCH QUESTIONS/PERSPECTIVES

- Determine whether arithmetic adjustments to conventional FRAX estimates have to be made with knowledge of CKD G4-G5D.
- Define whether ROD subtypes associate with fracture risk
- Define the efficacy and safety of anti-osteoporosis agents (bisphosphonates, denosumab, PTH analogs, raloxifene, romosozumab) in patients with CKD G4-G5D,
- Better characterization of role of primary and secondary mineralization in ROD
- Compare bone strength in iatrogenic (eg bisphosphonates) vs idiopathic (e.g. CKD related) low bone turnover
- Define whether antiresorptive therapy in patients with adynamic bone disease (ABD) or low bone turnover confers harm. Otherwise stated, is the “harm” of giving antiresorptives to patients with ABD or low bone turnover real or just theoretical?

CONCLUSIONS

Less than 20% of all patients experiencing a fragility fracture receive therapy to reduce future fracture within the year following fracture[179]. The main reason for this care gap is that osteoporosis and post-fracture management are still considered a low priority among clinicians. The fragility fracture and osteoporosis care gap are most probably even higher in patients with CKD G4-G5D. In these patients, ROD is thought to play a dominant role and benefit-cost ratio of available therapeutics is thought to be low. Adhering Hippocrates oath "first, do not harm", many clinicians follow a "wait and see" approach. Recent insights question the appropriateness of this approach and may foster a paradigm shift with regard to osteoporosis care in CKD. First, as CKD is a state of premature ageing, features of primary osteoporosis may be prominent in CKD patients. The contribution of ROD to bone fragility, conversely, may have been overemphasized in the past. Second, high-level evidence with regard to the efficacy of available osteoporosis drugs in patients with CKD G4-G5D is lacking in patients with osteoporosis and CKD G4-G5D. However, absence of evidence does not equal evidence of absence of effect. Post-hoc analyses of large registration trials and data from small and uncontrolled trials suggest similar efficacy of common osteoporosis drugs in patients with CKD G4-G5D as in the general population. Third, there are no strong reasons to assume that the risk-benefit ratio of therapy with antiresorptive agents, being excellent in the general population, is different in patients with CKD G4-G5D. In an era of personalized medicine, the risk-benefit ratio of osteoporosis drugs should be evaluated case-by-case and discussed with the patient prior to initiation therapy.

The recent KDIGO CKD-MBD guidelines allow for a more liberal use of antiresorptive agents in patients with CKD G4-G5D[52] and several expert panels already presented algorithms for fracture risk screening and initiation of anti-fracture strategies in patients with CKD have been proposed[15;26;180]. Although none of these algorithms has been validated by outcome data, they may -together with this consensus paper- provide pragmatic guidance pending further evidence (***Figure 1***).

COI

The authors declare that the results presented in this paper have not been published previously in whole or part, except in abstract format

TABLE 1: Clinical risk factors used for assessment of fracture probability

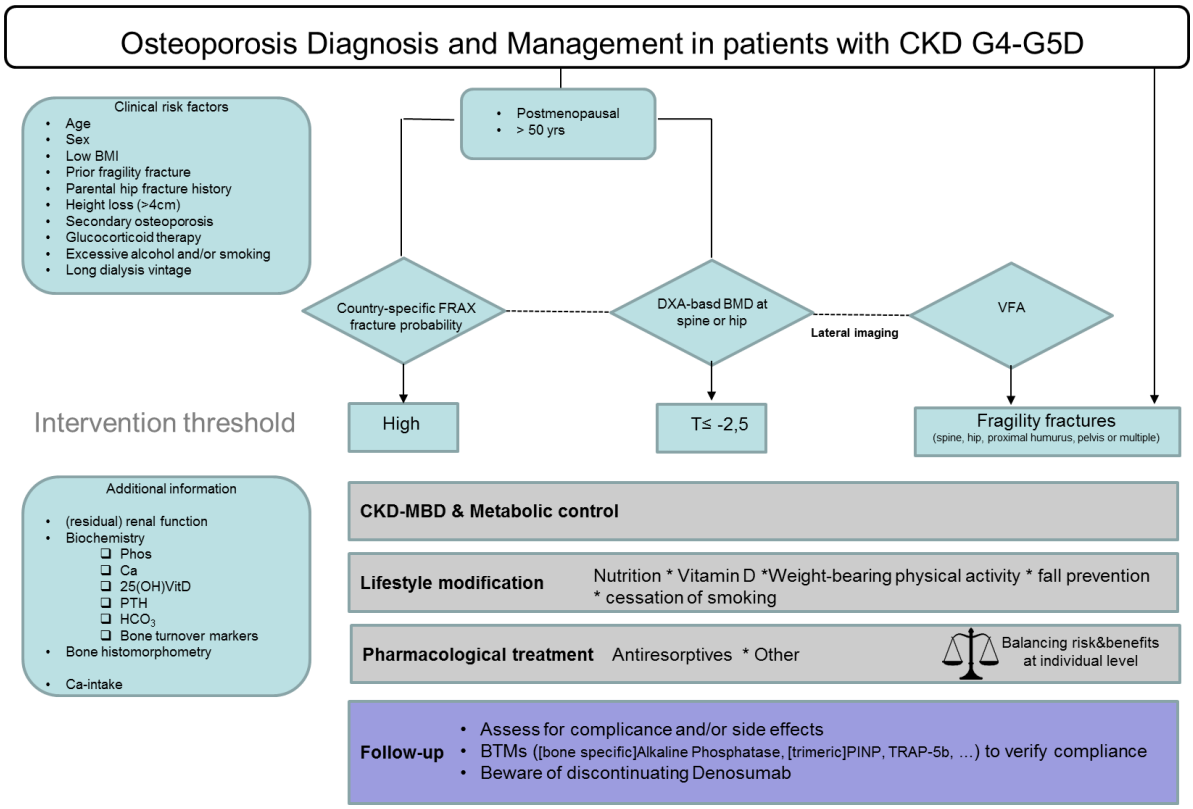
General risk factors
High Age
Sex (female)
Low body mass index
Previous fragility fracture, particularly of the hip, wrist and spine including morphometric vertebral fracture in adult life
Parental history of hip fracture
Glucocorticoid treatment (> 5 mg prednisolone daily or equivalent for 3 months or more)
Current smoking
Alcohol intake 3 or more units daily
Causes of secondary osteoporosis
Rheumatoid arthritis
Untreated hypogonadism in men and women
Inflammatory bowel disease
Prolonged immobility
Organ transplantation
Type 1 and type 2 diabetes
Thyroid disorders, e.g. untreated hyperthyroidism, thyroid hormone suppressive therapy
Chronic obstructive pulmonary disease
HIV infection
CKD-related risk factor
Dialysis vintage

Table 2: Efficacy and safety of common osteoporosis drugs in the setting of CKD

	Renal retention	**Efficacy**			**Safety (postmenopausal women)**	**Comments**
		Preclinical	**Post-hoc (postmenopausal women)**	**Clinical trial (advanced CKD)**		
nitrogen-containing bisphosphonates (alendronate, ibandronate, risedronate and zoledronic acid)	yes[118;119]	Yes [129;157]	Fracture ↓[120-122]	BMD (↑)[123-127]	Atypical fracture, ONJ, oesophagitis, (hypocalcemia, renal dysfunction) [131;137-139]	Dose adjustments?
Denosumab	no[141]	yes[145]	Fracture ↓[142]	BMD ↑[126;143;144;147;156]	Atypical fracture, ONJ, hypocalcemia [138;143]	Beware: offset of effect[150]
PTH analogues (teriparatide, abaloparatide)	no	yes[157]	Fracture ↓[158;159]	BMD ↑, in pts with ABD or hyoparathyroidism	Hypotension[160]	Dose adjustments?, Therapy to be limited to max 2 yrs
Romosozumab	unlikely	Yes, low PTH only[162].	No data	No data	Cardiovascular adverse events ↑[165], (hypocalcemia)	Beware: offset of effect

Abbreviations: BMD: bone mineral density; ABD: adynamic bone disease; ONJ: osteonecrosis of the jaw

FIGURE 1: Pragmatic approach to patients with CKD G4-G5D and osteoporosis



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