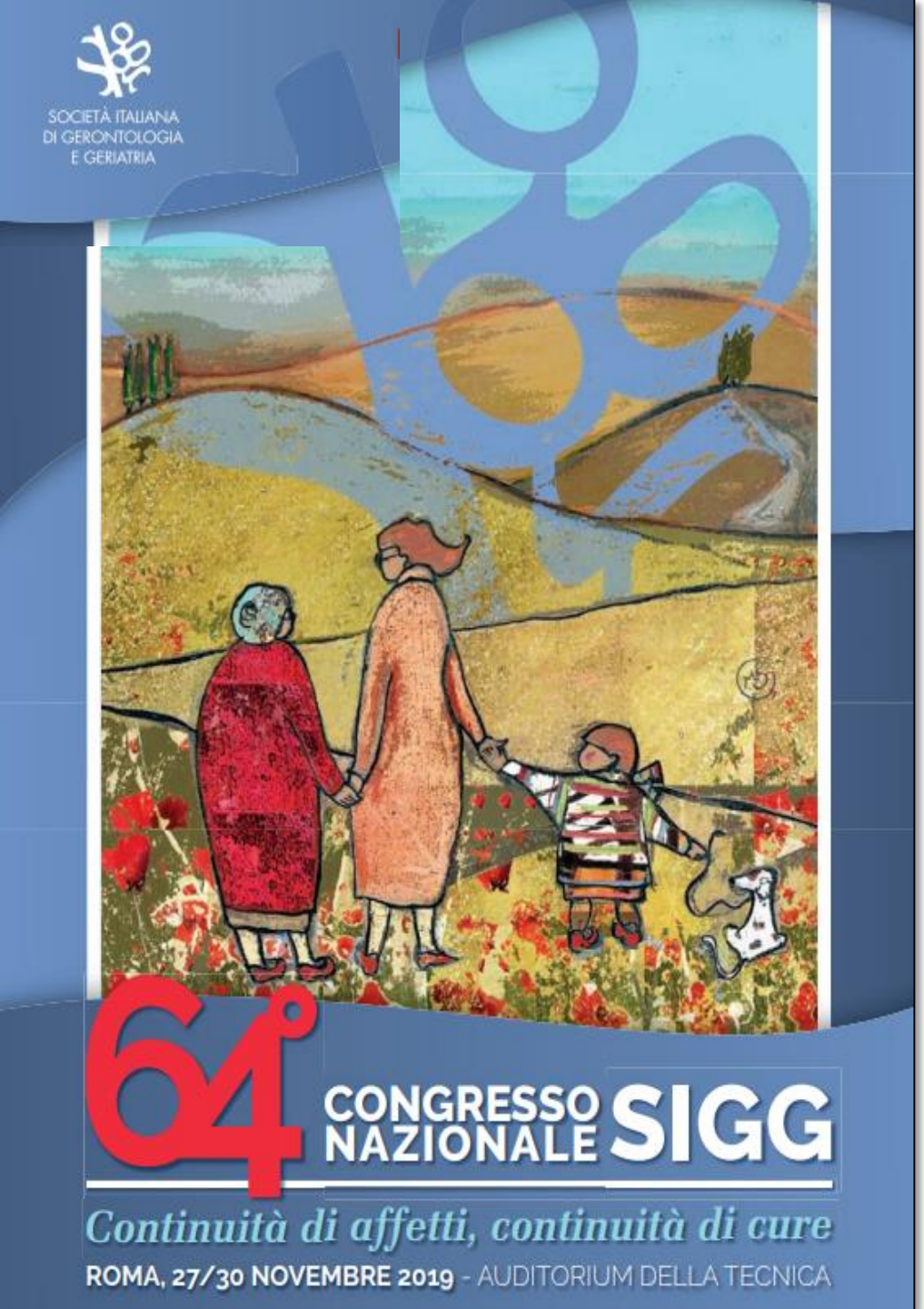

SAPIENZA
UNIVERSITÀ DI ROMA

AZIENDA OSPEDALIERA
SANT' ANDREA
FACOLTÀ DI MEDICINA E
PSICOLOGIA

QUALE TERAPIA PER IL PAZIENTE ANZIANO CON IRC E FRATTURE DA FRAGILITÀ

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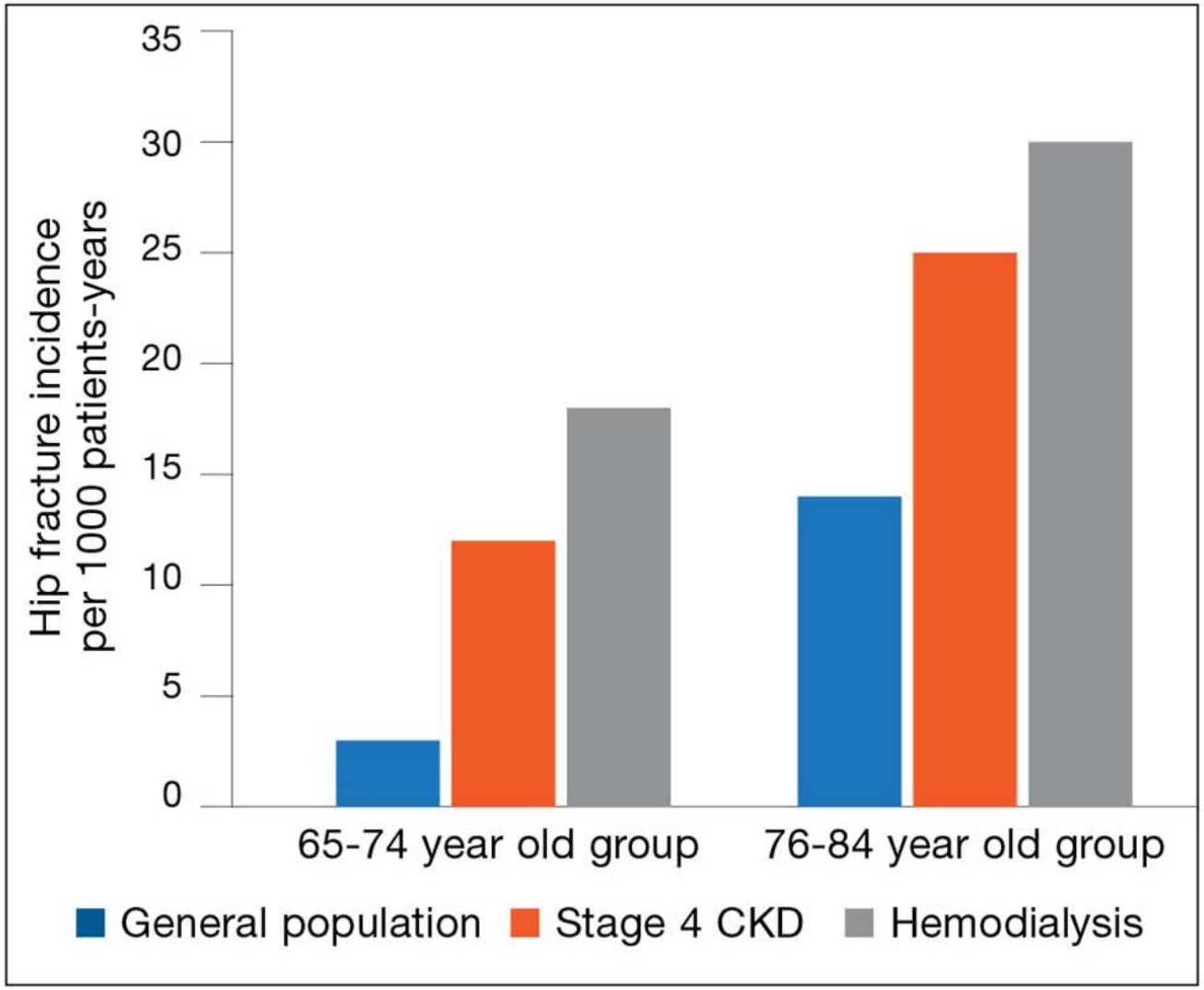
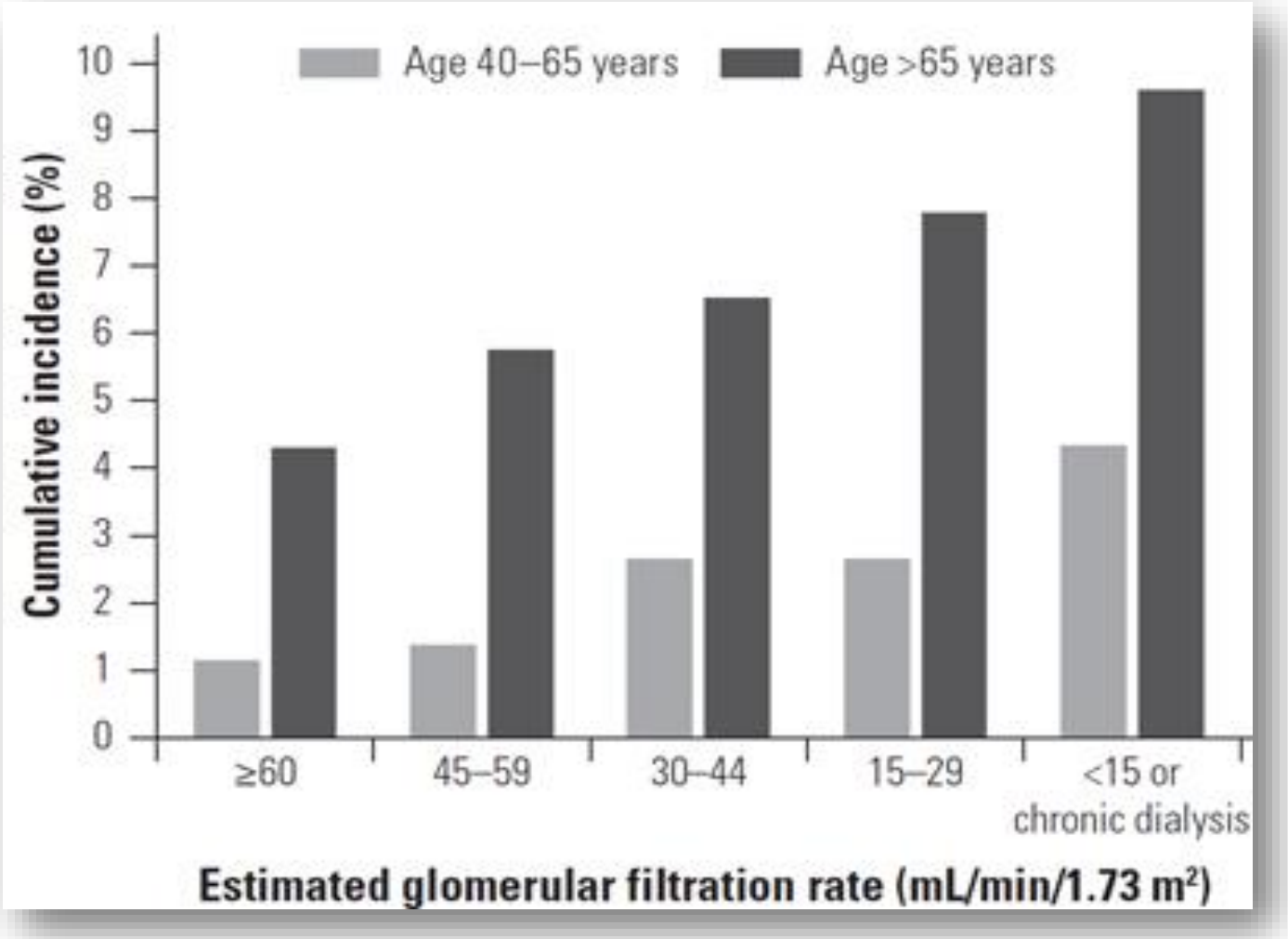
In ottemperanza alla normativa ECM ed al principio di trasparenza delle fonti di finanziamento e dei rapporti con soggetti portatori di interessi commerciali in campo sanitario, si informano i discenti che negli ultimi due anni non ho avuto i seguenti rapporti anche di finanziamento con soggetti portatori di interessi commerciali in campo sanitario

CKD Progression Increases Incidence of Hip Fracture



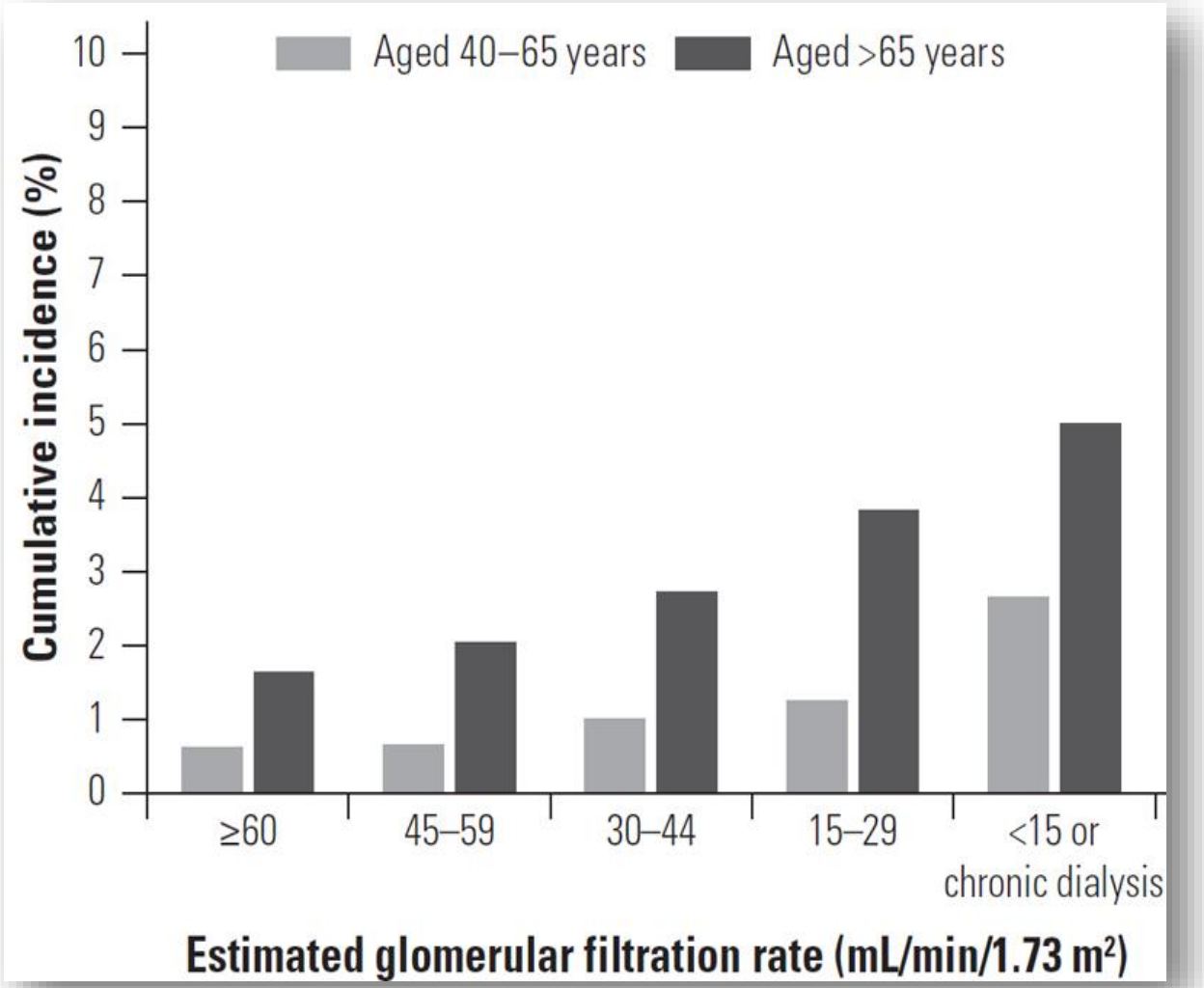
Moe and Nickolas. *CJASN.* 2016

Three-year cumulative incidence of fracture in women by Kidney function



Naylor et al 2014

Three-year cumulative incidence of fracture in men by Kidney function



Naylor et al 2014

Differences between CKD-MBD and Postmenopausal Osteoporosis

Clinical factor	CKD–MBD	Postmenopausal osteoporosis
PTH levels	Increased	Normal
Alkaline phosphatase	Increased	Normal
Bone mineral density	Weakly related to fracture risk	Predicts risk of fracture
Bone loss	Mostly in cortical bone	Trabecular and cortical bone
Bone formation rate	Either very low (in adynamic bone disease) or very high	Generally normal or slightly increased
Vascular calcification	Strongly associated	Weakly associated
Laboratory findings*	Abnormal	Normal or mildly abnormal

*Including levels of Ca^{2+}, phosphate, FGF-23, BMP-7, Klotho, 1,25-hydroxyvitamin D3, iron, bicarbonate, sclerostin, and cytokines. Abbreviations: BMP, bone morphogenetic protein; CKD–MBD, mineral bone disease in chronic kidney disease; FGF, fibroblast growth factor; PTH, parathyroid hormone.

Motivi della scarsa predittività della DXA sulle fratture nella CKD

Sovrastima della BMD
Calcificazioni aortiche
Artrosi e calcificazioni articolari
Deformità della colonna dovute
Alterazioni ossee qualitative e quantitative
Disposizione delle trabecole ossee
Densità di mineralizzazione non uniforme
Deposizione di cristalli ed altri metalli nella matrice ossea

La prevenzione primaria può essere difficile ma…non la secondaria!

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Classificazione istologica dell'osteodistrofia renale (ROD)

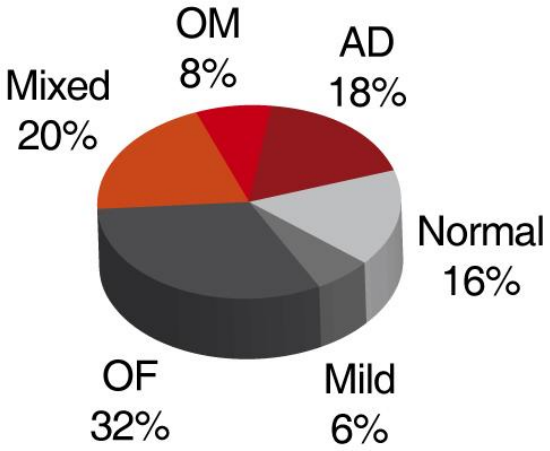
Sottotipo ROD	Turnover Osseo	Mineralizzazione Ossea
Osteite Fibrosa	Alto	Normale
Osteomalacia	Normale	Bassa
Malattia Adinamica Osso	Basso	Normale
Osteopatia Mista	Alto	Bassa

Tabella 1. Classificazione istologica dell'osteodistrofia renale (ROD). Modificato da Rossini M, et al *Guidelines for the diagnosis, prevention and management of osteoporosis*. Reumatismo 2016; 68:1-39

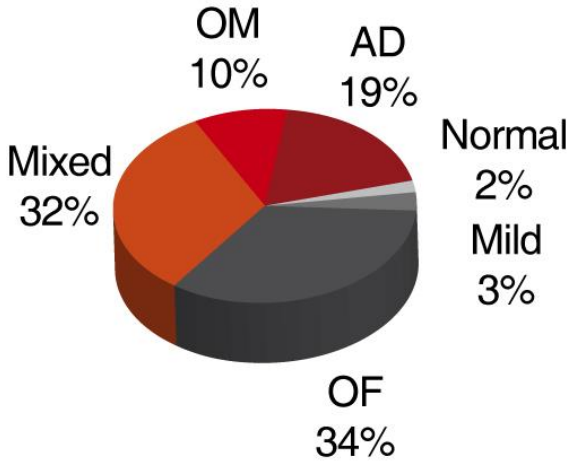
Linne guida SIOMMMS, Reumatismo, 2016

Cronich Kidney Disease and Bone Mineral Disorder (CKD-MBD) Incidence

CKD stage 3-5

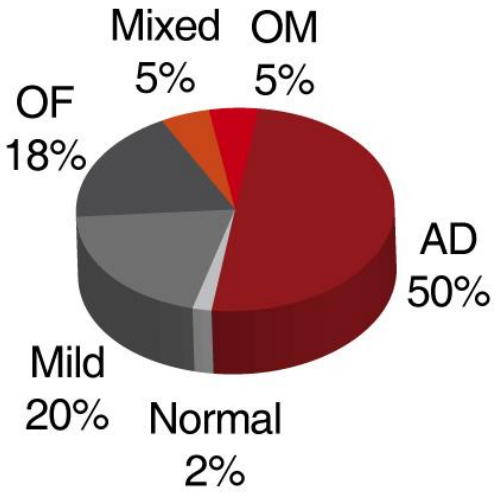


Hemodialysis



Lesione istologica
Osteite Fibrosa
Osteomalacia
Osteopatia Mista
Osso Adinamico

Peritoneal dialysis



Kidney International , 2009

Paratormone e Fosfatasi alcanina e diagnosi differenziale della CKD-MBD

DISORDER	SERUM INTACT PARATHYROID HORMONE	BONE-SPECIFIC ALKALINE PHOSPHATASE
Hyperparathyroidism		
Mild	200–400 pg/mL	Normal
Moderate	350–800 pg/mL	Normal or elevated
Severe	> 700 pg/mL	Elevated
Aluminum bone disease	10–500 pg/mL (mostly < 100)	Normal
Adynamic bone disease	< 100–150 pg/mL	Normal to low
Osteomalacia	Normal or mildly elevated	Mildly elevated

In groups of patients, the parathyroid hormone and bone-specific alkaline phosphatase levels can distinguish the various histologic forms of renal osteodystrophy. In individual patients, however, the values often overlap.

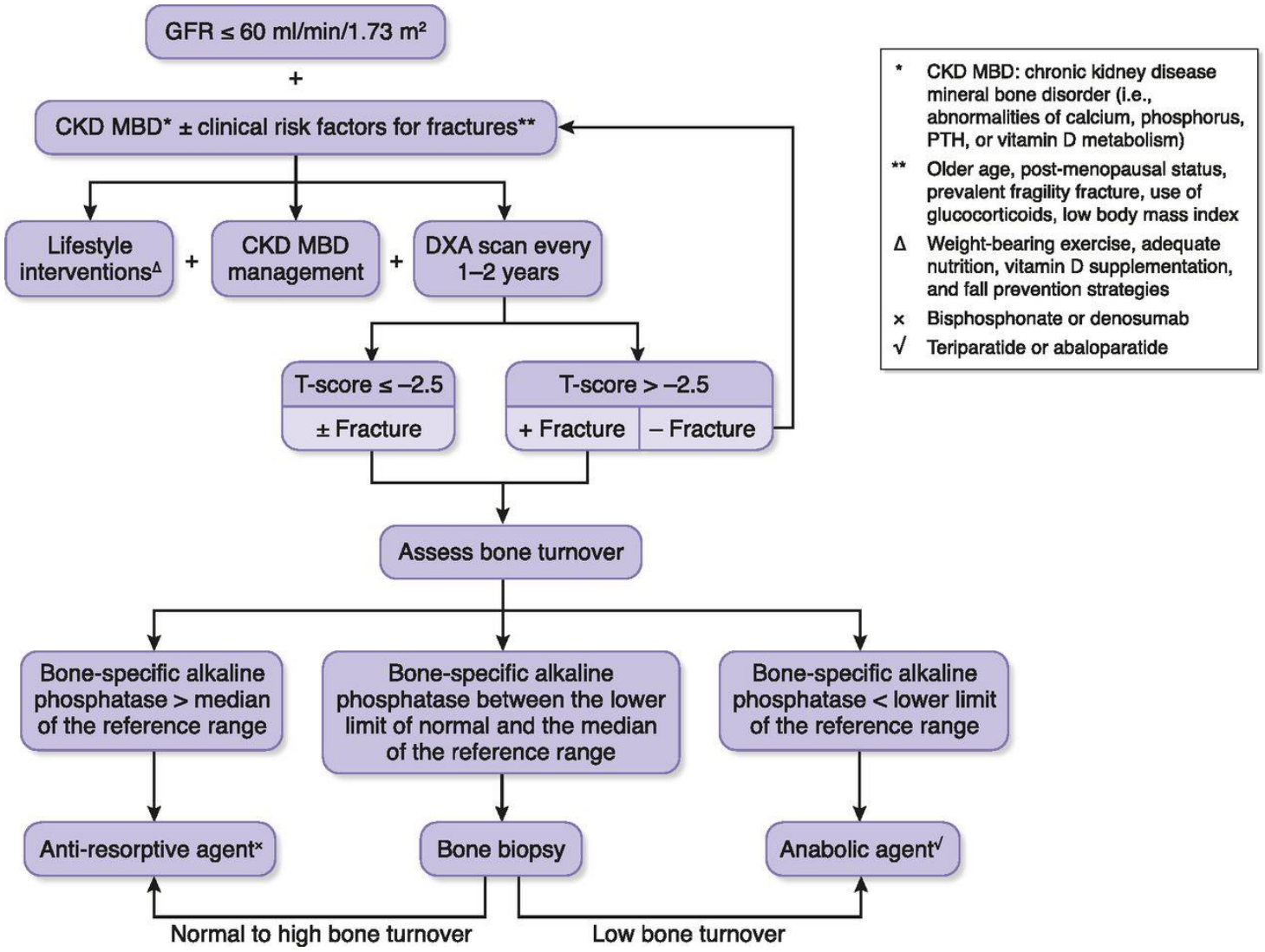
Miller PD, Lerma EV, 2005

Stadiazione della IRC e trattamento con farmaci per osteoporosi

Categorie di VGF (ml/min/ 1.73m²) Descrizione e livello			
	G1	Stesso trattamento della popolazione generale	≥90
	G2		60-89
	G3a		45-59
	G3b		30-44
	G4	Severamente ridotto	15-29
	G5	Insufficienza renale	<15

KDIGO CKD-MBD 2017

Management of Osteoporosis in CKD



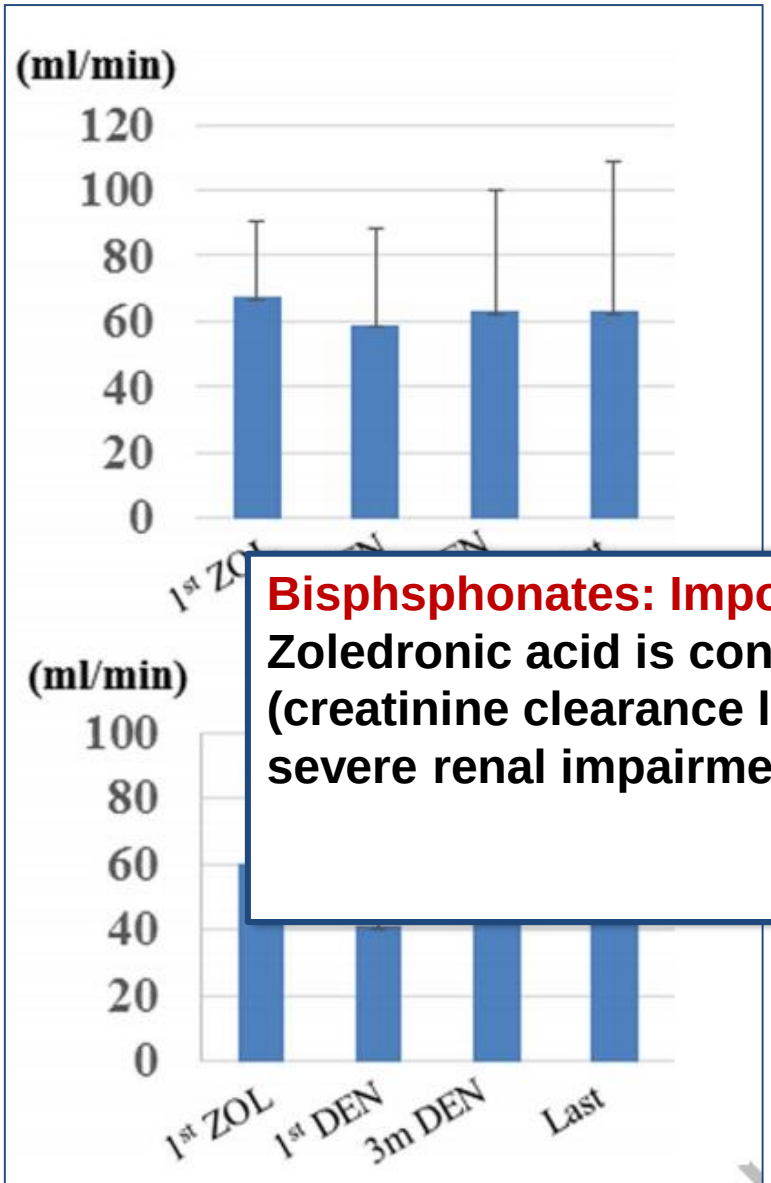
Clin J Am Soc Nephrol, 2018

Farmaci antiosteoporotici e IRC

Drugs	Dosage	FDA-Approved eGFR Cutoffs	Effect on Mineral Metabolism
Alendronate	70 mg PO once weekly	eGFR≥35 ml/min	Hypocalcemia, hypophosphatemia
Ibandronate	150 mg PO once monthly or 3 mg iv every 3 mo	eGFR>30 ml/min	—
Risendronate	5 mg PO daily or 35 mg PO weekly	eGFR>30 ml/min	Hypocalcemia, hypophosphatemia, increased PTH levels
Abaloparatide	80 μg Subcutaneously once daily	Any eGFR, not studied in ESKD	Hypercalcemia, hypercalciuria
Teriparatide	20–40 μg Subcutaneous daily	eGFR>30 ml/min	Hypercalcemia, hypocalcemia, hypercalciuria
Denosumab	60 mg Subcutaneous every 6 mo	Any eGFR	Hypocalcemia, hypophosphatemia
Romosozumab	210 mg Subcutaneous monthly	Not studied in CKD	—

FDA, Food and Drug Administration; PO, per oral; iv, intravenous; —, unknown PTH, parathyroid hormone.

Improvement of renal function by changing the bone-modifying agent from zoledronic acid to denosumab



Conclusions

For the first time, we demonstrated that the renal function of some patients, which had deteriorated following zoledronic acid administration, successfully improved after changing to denosumab.

Bisphsphonates: Importants Warnings

Zoledronic acid is controindicate in impaired renal function (creatinine clearance less than 35 mL/min); warning: patients with severe renal impairment should use oral drugs with caution

Endocrine Society Guideline, 2019

Int J Clin Oncol (2016) 21:1191–1195

Denosumab e CKD: work in progress

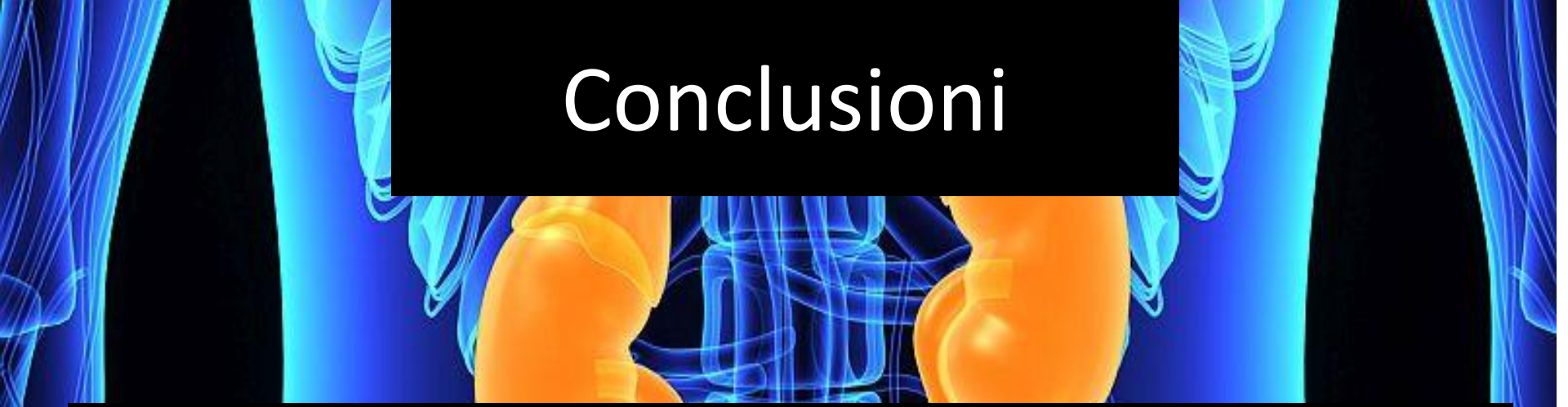
Majoor, 2019 [20]	Fibrous dysplasia	12	12-19	60 mg every 3 or 6 mo	Reduce in pain Decrease in BTM	Transient sHPT No patient developed hypocalcemia Skin rash in one patient
Yassin, 2014 [23]	Thalassemia major	30	12	60 mg every 6 mo	Increase in LS and FN BMD Decrease in BTM	
Voskaridou, 2018 [24]	Thalassemia major	32 on Dmab vs. 31 on placebo	12	60 mg every 6 mo	Reduce in pain Increase in LS and radius BMD Decrease of BTM	Randomized controlled trial
Chen, 2014 [34]	CKD/sHPT	12 on Dmab vs. 8 no treatment	-	Single injection of 60 mg	Increase in LS and FN BMD Decrease in bone pain Decrease in PTH levels	4 patients developed symptomatic hypocalcemia
Chen,						ed
Hirama [31]						
Cheng,						
Festuc [29]						ed
		alendronate		900 µg every 4 weeks	TRACP-5b (Dmab more effective)	
Bonani, 2016 [41]	Kidney transplantation	46 on Dmab vs. 44 on placebo	12	60 mg every 6 mo	Increase in LS, FN and TH BMD Increase in volumetric BMD and cortical thickness at the distal tibia and radius in HR-pQCT No Dmab effect on graft rejection	Randomized controlled trial Higher rates of hypocalcemia and urinary tract infections with Dmab
Maehana, 2017 [43]	Kidney transplantation	4	12	60 mg every 6 mo	Increase in LS and FN BMD	
Brunova, 2018 [39]	Solid organ transplantation	63	20	60 mg every 6 mo	Increase in LS and FN BMD No effect on radius BMD	
Bonani, 2019 [40]	Kidney transplantation	23 on Dmab vs. 21 no treatment	12	60 mg every 6 mo	Increase in LS aBMD No significant effect on trabecular bone score	

Conclusion:

In this reported off-label use Dmab was generally well tolerated without major adverse events. A common adverse event is hypocalcemia. Based on these observations, is seems rational that calcium intake should be optimal and vitamin D levels are repleted before Dmab administration.

Bone, 2019

Conclusioni



- I pazienti anziani con fratture da fragilità ed IRC lieve moderata devono ricevere una terapia per la prevenzione secondaria delle fratture al pari degli altri pazienti
- Negli stadi avanzati bisogna escludere la presenza di una osteopatia adinamica dell'osso valutando PTH e ALP per valutare una terapia con anabolizzante (teriparatide) se VFG>30ml/min
- Il farmaco al momento più indicato negli stadi CKD 4 -5 è il Denosumab con evidenze in crescendo di efficacia e sicurezza