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Update on the clinical use of trabecular bone score (TBS) in the management of osteoporosis: results of an expert group meeting organized by the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO), and the International Osteoporosis Foundation (IOF) under the auspices of WHO Collaborating Center for Epidemiology of Musculoskeletal Health and Aging

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Abstract

Purpose Trabecular bone score (TBS) is a grey-level textural measurement acquired from dual-energy X-ray absorptiometry lumbar spine images and is a validated index of bone microarchitecture. In 2015, a Working Group of the European Society on Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO) published a review of the TBS literature, concluding that TBS predicts hip and major osteoporotic fracture, at least partly independent of bone mineral density (BMD) and clinical risk factors. It was also concluded that TBS is potentially amenable to change as a result of pharmacological therapy. Further evidence on the utility of TBS has since accumulated in both primary and secondary osteoporosis, and the introduction of FRAX and BMD T-score adjustment for TBS has accelerated adoption. This position paper therefore presents a review of the updated scientific literature and provides expert consensus statements and corresponding operational guidelines for the use of TBS.

Methods An Expert Working Group was convened by the ESCEO and a systematic review of the evidence undertaken, with defined search strategies for four key topics with respect to the potential use of TBS: (1) fracture prediction in men and women; (2) initiating and monitoring treatment in postmenopausal osteoporosis; (3) fracture prediction in secondary osteoporosis; and (4) treatment monitoring in secondary osteoporosis. Statements to guide the clinical use of TBS were derived from the review and graded by consensus using the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) approach.

Results A total of 96 articles were reviewed and included data on the use of TBS for fracture prediction in men and women, from over 20 countries. The updated evidence shows that TBS enhances fracture risk prediction in both primary and secondary osteoporosis, and can, when taken with BMD and clinical risk factors, inform treatment initiation and the choice of antiosteoporosis treatment. Evidence also indicates that TBS provides useful adjunctive information in monitoring treatment with long-term denosumab and anabolic agents. All expert consensus statements were voted as strongly recommended.

Conclusion The addition of TBS assessment to FRAX and/or BMD enhances fracture risk prediction in primary and secondary osteoporosis, adding useful information for treatment decision-making and monitoring. The expert consensus statements provided in this paper can be used to guide the integration of TBS in clinical practice for the assessment and management of osteoporosis. An example of an operational approach is provided in the appendix.

Summary This position paper presents an up-to-date review of the evidence base, synthesised through expert consensus statements, which informs the implementation of Trabecular Bone Score in clinical practice.

Keywords Trabecular bone score · TBS · Fracture · Osteoporosis · Guidelines

Eugene V. McCloskey and Nicholas C. Harvey are joint senior authors.

Introduction

Osteoporosis is conceptually defined as a systemic skeletal disease characterized by low bone mass and deterioration of bone microarchitecture, leading to bone fragility and a consequent increase in fracture risk [1, 2]. This definition encompasses the two pillars of bone resilience to fracture: bone mass (the amount of bone present) and bone microarchitecture (the material and organizational properties of bone). The densitometric assessment of osteoporosis is based on a bone mineral density (BMD) T-score of -2.5 or less, which captures the bone mass element of fracture risk and is effective in identifying some, but not all individuals who go on to experience a fragility fracture [3, 5, 6]. An important clinical challenge is that most fragility fractures occur in individuals who have a BMD T-score in the osteopenic or normal range and therefore fall below the originally defined densitometric interventional threshold [3–6]. Ideally, the skeletal assessment of bone fragility should also capture bone microarchitecture as the second pillar of fracture resilience in order to improve the identification of individuals at high risk of fracture.

Trabecular bone score (TBS) is a grey-level textural measurement usually acquired from conventional lumbar spine dual-energy X-ray absorptiometry (DXA) BMD images, which provides a validated index of bone microarchitecture and correlates with mechanical properties of bone [7–12]. The score may be used as a continuous variable, by adjusting FRAX probability or BMD T-score, and has been interpreted clinically with cut-off values at thirds of the distribution [13, 14]. In 2015, a review of the evidence for TBS in the assessment of osteoporosis was conducted by an Expert Working Group of the European Society on Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO) [15]. The review concluded that TBS predicts hip and major osteoporotic fracture risk, at least partly independent of BMD and clinical risk factors and that TBS is potentially amenable to change as a result of pharmacological therapy [15]. Since then, the evidence base has rapidly expanded, with advances in the understanding of the role of TBS for fracture risk assessment in secondary as well as primary osteoporosis, for example in type 2 diabetes [16–18]. Evidence has also accumulated on the added value of TBS for decisions on treatment initiation and in understanding the effects of different antiosteoporosis therapies on bone microarchitecture in conjunction with known mechanisms of action [19–24]. It is estimated that over 2 million TBS assessments are performed annually (data extrapolated from

Kanis et al., 2021) [25], with the clinical interpretation of results supported by FRAX® [13, 26] and BMD T-score adjustments for TBS [14]. Given this rapid expansion of the scientific literature and the increasing clinical adoption of TBS, the ESCEO and International Osteoporosis Foundation (IOF) convened a Working Group to review the updated evidence base and provide guidance on the integration of TBS into clinical practice. The Appendix presents practical suggestions relating to clinical implementation and technical issues, derived from the Expert Working Group statements, technical information and clinical experience.

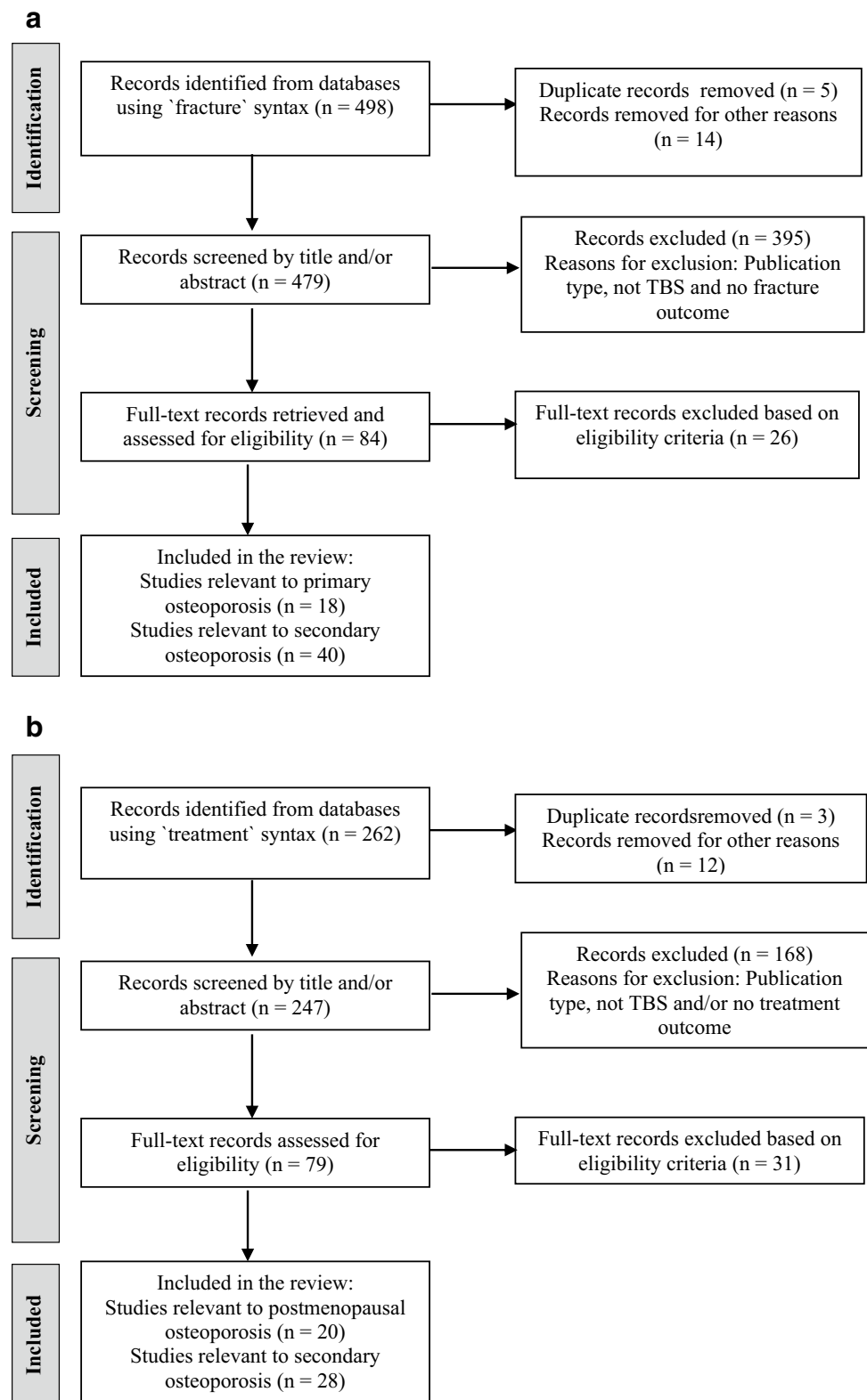
Methods

The international Expert Working Group included independent clinical scientists, physicians and researchers with expertise in the assessment, diagnosis and treatment of osteoporosis. Prior to the Working Group meeting, four topics were selected for review and systematic reviews of the evidence were undertaken: (1) use of TBS in fracture risk prediction; (2) use of TBS for treatment initiation and assessing response to pharmacological interventions in postmenopausal osteoporosis; (3) use of TBS for the assessment of fracture risk in secondary osteoporosis; and (4) use of TBS for assessing response to pharmacological therapies in secondary osteoporosis.

Systematic review search strategy

A comprehensive literature search was conducted using a similar approach to PRISMA guidelines, for articles published in MedLine via PubMed [27]. Fracture syntax (topics 1 and 3, Fig. 1a) comprised ‘trabecular bone score’ OR ‘TBS’ [search term(Title/Abstract)], AND ‘fracture(s)’ [search term(Title/Abstract)]. Treatment syntax (topics 2 and 4, Fig. 1b) comprised ‘trabecular bone score’ OR ‘TBS’ [search term(Title/Abstract)], AND ‘treatment(s)’ AND ‘effect’ [search term(Title/Abstract)], OR ‘therapy(ies)’ [search term(Title/Abstract)], OR ‘trial’ [search term(Title/Abstract)] AND ‘effect’ [search term(Title/Abstract)]. Articles were considered for review if they met the following general screening criteria: (i) an original, full-text study with TBS as a primary outcome, (ii) published or *in-press* (or known ‘accepted’ status and shared by a co-author) between March 2015 and 9th February 2023, and (iii) available in the English language. Further eligibility criteria were specific to each of the four topics. A total of 96 papers were reviewed by 2 independent reviewers.

Fig. 1 **a** PRISMA flow diagram of the literature search process for studies investigating trabecular bone score (TBS) and fracture prediction in primary and secondary osteoporosis. **b** PRISMA flow diagram of the literature search process for studies investigating trabecular bone score and treatment monitoring in postmenopausal and secondary osteoporosis



Expert consensus statements and operational guidelines

Expert consensus statements were developed in accordance with the Grades of Recommendation, Assessment,

Development and Evaluation (GRADE) approach [28]. The GRADE approach is a widely used method for evaluating the quality of evidence and developing clinical recommendations. It provides a systematic and transparent

process for assessing the certainty of the evidence, balancing the benefits and harms of interventions, and formulating recommendations. The GRADE approach involved several key steps:

1. Identifying the clinical questions: The first step involved defining the clinical questions regarding TBS, that the recommendations were to address. This included specifying the population and outcomes of interest.
2. Assessing the quality of evidence: the quality of evidence for each outcome was assessed using a systematic approach, with a defined study eligibility criteria, and considering methodological factors.
3. Rating the certainty of evidence: the certainty of evidence was characterized according to four levels: good, moderate, low, or very low. This rating reflects the confidence that the evidence accurately represented the true effect of TBS on a given outcome.
4. Formulating recommendations: a consensus process was followed to develop recommendations. The International Working Group, consisting of experts in the field, considered the quality and certainty of the evidence, the balance between benefits and harms, clinical experience, practical and resource implications, and other relevant factors.
5. Grading the strength of recommendations: a level of strength was assigned to each recommendation, indicating the extent to which the Working Group believes the benefits of the intervention outweigh the potential harms. Recommendations could be classified as either strong or weak.

The primary purpose of the GRADE approach is to help clinicians, researchers, and guideline developers make informed decisions based on the available evidence while considering various factors that may influence clinical practice. The process included a face-to-face meeting of the Working Group on 9th February 2023 with presentations on each topic. Following the GRADE approach and based on the discussions and review outcomes, 22 corresponding statements were developed to inform guidance on the use of TBS in clinical practice. Thereafter, operational guidance to support the integration of TBS in clinical practice was developed.

Results

Topic 1: Use of TBS in fracture risk prediction in postmenopausal and male osteoporosis

Eighteen studies met the eligibility criteria (prospective study design, conducted in men and/or women aged 40 years or over; Fig. 1a). Of these, one study was conducted in Australia [29],

five in Canada [14, 30–33], two in China [34, 35], two in Japan [36, 37], one in Korea [38], one in Slovakia [39], three in Switzerland [40–42], one in Thailand [43], and two in the USA [44, 45]. Cohort sizes from different ethnicities ranged from 115 to 45,185, and follow-up from 2.7 to 10 years. Ten studies were conducted in postmenopausal women, five in men, and three in both men and women, with mean age ranging from 58 to 76 years. The incident fracture rates for major osteoporotic fractures (MOF, including hip) ranged from 1.2 to 14%, and for vertebral fractures, 3.5 to 35% (Table 1). TBS was an independent predictor of incident fracture in 16 of 18 studies (Table 1). For each SD reduction in TBS, the increased risk of incident fracture ranged from 19% [14] to more than double [39, 40]. The combination of TBS and BMD significantly enhanced the prediction of fracture risk compared to lumbar spine BMD in men and women [27, 40–42, 44], although, in one study, this was only significant in men [34].

TBS-adjusted FRAX

In 2016, a meta-analysis of 14 prospective population cohort studies showed that TBS is a significant predictor of fracture risk independent of FRAX and that the adjustment of FRAX for TBS resulted in a small but significant increase in fracture risk prediction, independent of gender and ethnicity [13]. The impact of TBS adjustment on FRAX probabilities is dependent on age, femoral neck BMD and the FRAX probability value [46]. Since 2016, four further prospective studies in women [14, 30, 37, 41] and three in men [35, 36, 44] have since demonstrated that TBS combined with FRAX enhances the prediction of MOF, hip and vertebral fracture, compared with FRAX alone. Used together, the global assessment of fracture risk considers bone mass, bone microarchitecture and clinical risk factors (CRF). One recent study examined whether antiresorptive treatment affects fracture risk prediction from TBS using a large clinical registry ($n=76,810$) that includes all DXA tests for the Province of Manitoba, Canada. Results showed that TBS was a robust predictor of fracture in models adjusted for clinical risk factors and BMD and that the use of antiresorptive treatment (mostly bisphosphonates) either in the year before or following TBS measurement (mean total use, 5.6 years) did not attenuate fracture risk prediction [33].

Over a 10-year follow-up period in 1541 Japanese women (mean age 58 y) [37], every SD increase in TBS-adjusted FRAX score equated to a 46% increased risk of fracture (OR: 1.46, 95%CI 1.08, 1.98) compared to 35% with FRAX alone (OR: 1.35, 95%CI 1.09, 1.67). Similar results were found in the Fujiwara-Kyo Osteoporosis Risk in Men (FORMEN) study [36], and in Chinese men from the MrOs. Hong Kong cohort [35]. In the latter, when applying the Taiwan Intervention Strategy treatment threshold

Table 1 Trabecular bone score (TBS) for prediction of fracture risk in men and women aged ≥ 40 years

First author, year	Location	Follow-up, years	Subjects	TBS software version	Outcome(s)	TBS HR, OR/SD change (95%CI)	FRAX or BMD HR, OR/SD change (95%CI)	TBS with FRAX or BMD HR, OR/SD change (95%CI)	Adjustments
Iki 2015 [36]	Japan	4.5	1805 men (mean age 73 y)	2.1	MOF	1.89 (1.28, 2.81)	1.35 (1.02, 1.80) ^{FRAX}	1.41 (1.15, 1.74) ^{FRAX}	FRAX
Popp 2016 [40]	Switzerland	2.7	556 PM women	1.8.2	MOF	2.01 (1.54, 2.63)	1.58 (1.16, 2.10) ^{LS BMD}	1.78 (1.26, 2.50) ^{LS BMD}	Age, BMD, BMI
Schousboe 2016 [44]	USA	8.6	5863 men (mean age 74 y)	2.1	MOF Hip fracture	1.23 (1.14, 1.37) 1.06 (0.88, 1.28)	NR NR	1.31 (1.20, 1.43) ^{FRAX} 1.24 (1.08, 1.43) ^{FRAX}	FRAX
Martineau 2017 [30]	Canada	8.7	34,316 PM women	2.1	MOF Hip fracture	1.20 (1.16, 1.24) 1.13 (1.06, 1.21)	NR	1.17 (1.13, 1.22) ^{FRAX} 1.14 (1.06, 1.22) ^{FRAX}	FRAX
Su 2017a [34]	China	MsOs 8.8 MrOs 9.9	1950 PM women 1923 men (mean age 73 y)	2.1	MOF – women MOF – men	1.60 (1.17, 2.20) 3.04 (1.92, 4.81)	NR	NR	Age
Su 2017b [35]	China	MsOs 8.8 MrOs 9.9	1950 PM women 1923 men (mean age 73 y)	2.1	MOF – women MOF -men	1.32 (1.13, 1.54) 1.38 (1.15, 1.65)	1.35 (1.24, 1.48) ^{FRAX} 1.58 (1.40, 1.79) ^{FRAX}	1.39 (1.27, 1.52) ^{FRAX} 1.65 (1.45, 1.86) ^{FRAX}	FRAX
Schousboe 2017 [45]	USA	4.6	5831 men (mean age 72 y)	2.1	Clinical VF Radio-graphic VF	1.62 (1.42, 1.84) 1.41 (1.23, 1.63)	2.50 (2.09, 3.00) ^{LS BMD} 1.95 (1.63, 2.34) ^{LS BMD}	1.19 (1.02, 1.38) ^{LS BMD} 1.11 (0.94, 1.30) ^{LS BMD}	Age, BMI, BMD
Leslie 2018 [14]	Canada	7.4	45,185 women (mean age 64 y)	2.1	MOF Hip fracture	NR	1.41 (1.36, 1.46) ^{LS BMD} 1.17 (1.09, 1.25) ^{LS BMD}	1.48 (1.42, 1.53) ^{LS BMD} 1.33 (1.23, 1.44) ^{LS BMD}	Age, BMI, FRAX CRFs
Martineau 2018 [30]	Canada	8.7	37,176 men and women (mean age 64 y)	2.1	MOF Hip fracture	1.19 (1.15, 1.23) 1.13 (1.05, 1.20)	NR	NR	Age, BMI FRAX CRFs
Kužma 2018 [39]	Slovakia	5.2	127 PM women	1.9.1	MOF	2.1 (0.79, 5.9)	2.79 (1.11, 7.05) ^{FRAX}	3.09 (1.22, 7.8) ^{FRAX}	10% MOF, 1.5% Hip and < 1.31 TBS thresholds applied
Tamaki 2019 [37]	Japan	10	1541 PM women	1.9.2	MOF	NR	1.35 (1.09, 1.67) ^{FRAX}	1.46 (1.08, 1.98) ^{FRAX}	FRAX
Shevroja 2019 [41]	Switzerland	4.4	1362 PM women	3.03 vs. 4.0	Self-report MOF	1.43 (1.12, 1.83) V3 1.54 (1.18, 2.00) V4	NR	NR	Age, osteoporotic treatment, BMD
Li 2020 [32]	Canada	7.5	2730 PM women	2.1	MOF	1.50 (1.31, 1.71)	NR	1.38 (1.21, 1.59) ^{FRAX}	Age, FRAX
Kim 2020 [38]	Korea	7.5	1165 women (age 45–76 y)	2.0.1	Self-report MOF Hip fracture	1.16 (0.83, 1.62) NR	1.06 (0.98, 1.05) ^{FRAX} 1.01 (0.99, 1.03) ^{FRAX}	Not given 1.01 (0.99, 1.03) ^{FRAX}	FRAX CRFs

Table 1 (continued)

First author, year	Location	Follow-up, years	Subjects	TBS software version	Outcome(s)	TBS HR, OR/SD change (95%CI)	FRAX or BMD HR, OR/SD change (95%CI)	TBS with FRAX or BMD HR, OR/SD change (95%CI)	Adjustments
Shevroja 2022 [42]	Switzerland	4.4	1632 PM women	4.0	MOF_L1L3	1.64 (1.34, 2.00)	1.32 (1.15, 1.53) ^{LS BMD}	NR	Age, BMD
					MOF_L1L4	1.60 (1.32, 1.95)	1.30 (1.14, 1.48) ^{LS BMD}		
					VF_L1L3	1.70 (1.34, 2.16)	1.33 (1.08, 1.63) ^{LS BMD}		
					VF_L1L4	1.68 (1.32, 2.13)	1.38 (1.17, 1.62) ^{LS BMD}		
Leslie 2023 [33]	Canada	8.6	4838 (cohort 1) and 5536 (cohort 2) PM women with high adherence to BP	3.03	MOF	1.31 (1.20, 1.43)	NR	1.22 (1.12, 1.34) ^{FN BMD}	All covariates including FN BMD
					Hip fracture	1.49 (1.27, 1.76)		1.35 (1.14, 1.59) ^{FN BMD}	
					Any fracture (Reported at 2 nd visit)	1.28 (1.12, 1.31)		1.21 (1.12, 1.31) ^{FN BMD}	
Sakulpisuti 2022 [43]	Thailand	5	115 men (mean age 69 y)	2.1	Radio-graphic VF	1.30(1.07, 1.58)	1.03 (0.80, 1.32) ^{LS BMD}	NR	Age, BMD

BMD, bone mineral density; *BP*, bisphosphonate therapy; *FN*, femoral neck; *LS*, lumbar spine; *MOF*, major osteoporotic fracture; *NR*, not reported; *PM*, postmenopausal; *TBS*, trabecular bone score; *VF*, vertebral fracture

Note: One study did not report odds ratio (OR), hazards ratio (HR) or relative risk for TBS, or any adjustments with TBS [29]. The results of this study, presented as AUC, are included in Table Sa (supplementary information)

of 12.5% [47], TBS-adjusted FRAX improved the net risk classification by 5.2% compared to FRAX without TBS [35]. These findings are consistent with those in Caucasian men and women [44, 48, 49].

In 5863 men (mean age 73.7 y) from the MrOS cohort, over 8.6 years [44], TBS significantly predicted incident MOF and hip fracture, independent of FRAX with BMD, and prevalent radiographic vertebral fracture. For each SD reduction in TBS, there was a 27% (HR: 1.27, 95%CI 1.17, 1.39) and 20% (HR: 1.20, 95%CI 1.05, 1.39) greater risk of MOF and hip fracture, respectively. Using the 20% National Osteoporosis Foundation (NOF, now the Bone Health Osteoporosis Foundation, BHOF) treatment threshold, [50] the addition of TBS to FRAX also increased the Net Reclassification Index (NRI) by 3.3%, and with TBS, FRAX and prevalent radiographic vertebral fracture, the NRI increased further to 6.2%.

Similar results were found in 34,316 women from the Manitoba cohort (mean age 63.5 y), over 8.7 years [30]. The NRI with TBS-adjusted FRAX was computed using treatment thresholds from three clinical guidelines: Bone Health and Osteoporosis Foundation (BHOF) [50], Osteoporosis Canada [51] and the UK National Osteoporosis Guideline Group [52]. For all thresholds, the TBS

adjustment had a positive effect in identifying fracture cases. In the overall group, TBS-adjusted FRAX yielded a small but significant increase in the NRI (NRI = 3.5% $p = 0.002$) compared with FRAX alone. Most reclassification occurred in individuals with a non-osteoporotic T-score (NRI = 3%), and there was also an age interaction, with reclassification more frequent in women under 65 years of age (NRI = 5.6%, $p < 0.001$). Consistent with findings elsewhere reporting up to 25% reclassification [14, 48, 49, 53] and as expected, most reclassification (> 90%) occurred for women close to an intervention cut-off (range 9 to 17.9%), suggesting that the clinical utility of TBS (i.e. altering risk classification and hence intervention decisions) is particularly enhanced when targeted to this segment of the population.

TBS-adjusted BMD T-score

The adjustment of BMD T-score for TBS represents a clinically relevant advancement in the field, deriving from the analysis of the Manitoba cohort of 45,185 women (mean age 63.5 y) on GE DXA systems [14] and confirmed in the OsteoLaus cohort using a Hologic DXA system [54]. In the Manitoba cohort at follow-up (mean 7.4 y), 3925 of

women (8.7%) had sustained at least one incident MOF, and 1040 (2.3%) had sustained at least one incident hip fracture [14]. Each SD decrease in TBS was significantly associated with a 26%, 25% and 22% greater risk of MOF in models incorporating BMD at the lumbar spine, femoral neck and total hip, respectively, and the results were not attenuated after adjustment for age and BMI. Using risk estimates from the Cox proportional hazards models, the authors applied a risk-equivalent offset adjustment to BMD T-scores to derive TBS-adjusted BMD T-scores for each site (spine, neck and total hip). There were significant improvements in fracture risk prediction using the TBS-adjusted BMD T-scores, compared to the unadjusted T-scores. Of relevance when FRAX is the primary approach, the study also confirmed the strong agreement in fracture probability scores between the TBS-adjusted FRAX tool, and when using TBS-adjusted femoral neck BMD T-score as the BMD input to FRAX ($r^2 = 0.98$, slope = 1.02, intercept = -0.3).

The combination of TBS with BMD for fracture prediction has been examined in the Swiss Evaluation of Methods of Measurement of Osteoporotic Fracture Risk (SEMOF) cohort study of 556 older women (mean age 76.1 y). Here, TBS significantly predicted incident fracture, independent of BMD (HR = 2.01, 95%CI 1.54, 2.63) [40]. The combination of TBS with lumbar spine BMD or the lowest BMD, significantly enhanced fracture prediction, with significantly different areas under the receiver operator curve (AUC) compared to models without TBS. Compared to osteoporosis (58%) or degraded TBS (60%) alone, the combination of osteoporosis and degraded TBS improved the classification of women with an osteoporotic fracture to 77%, confirming findings elsewhere in postmenopausal women [55] and non-osteoporotic patients [56]. Degraded TBS was categorized using data from a meta-analysis [13], where L1 to L4 TBS risk thresholds were established using a gender-independent tertile approach, with cut-off values for TBS of 1.23 and 1.31. Those with TBS values above 1.31 were characterised as being at low risk of fracture, those between 1.31 and 1.23 at intermediate risk and, finally, those below 1.23 at high risk of fracture. In subsequent studies, and in clinical usage, these tertiles have been termed normal TBS, partially degraded TBS and degraded TBS respectively.

Overall, whilst FRAX is widely available, and indeed is incorporated into over 100 guidelines internationally, some national guidelines predicate treatment on the basis of T-score rather than absolute fracture probability [57]. Furthermore, FRAX models are not available for all countries or territories. In these settings, the use of TBS-adjusted BMD T-score provides a practical method in which TBS information can be incorporated into risk assessment approaches.

Statements (GRADE outcome: strongly recommended)

The expert Working Group made the overall recommendation that TBS should be used in conjunction with BMD and clinical risk factors. Individual statements, all of which were strongly supported by the members of the Working Group, are itemized below:

1. TBS is predictive of fragility fractures in postmenopausal women and men above the age of 50 years.
2. TBS is predictive of fragility fractures independent of BMD and of clinical risk factors (including those in FRAX).
3. TBS adds predictive value when used in association with FRAX and BMD to adjust the FRAX probability of fracture in postmenopausal women and in men above the age of 50 years.
4. BMD adjusted for TBS is an alternative solution when FRAX is not available.
5. The greatest utility of TBS is for those individuals who lie close to a FRAX or BMD T-score intervention threshold.
6. TBS continues to add value to FRAX in patients previously receiving antiresorptive treatments.

Topic 2: Use of TBS for the initiation of treatment and monitoring of treatment effect in postmenopausal osteoporosis

Twenty studies met the eligibility criteria (prospective or intervention trial of an antiosteoporosis treatment in postmenopausal women, ≥ 6 months treatment duration; Fig. 1b), and six were international multi-centre trials. Of those remaining, two were conducted in Canada, two in Japan, two in India, four in South Korea, one in Spain, one in Taiwan and two in the USA. Cohort sizes ranged from 28 to 6985 and treatment duration, from 6 months to 10 years. Studies included antiresorptive treatments anabolic treatments, and/or sequential treatment and/or treatment combinations (Table 2).

Antiresorptive agents

Antiresorptive treatment studies included bisphosphonates, menopausal hormone therapy (MHT), selective estrogen receptor modulators (SERMs) and denosumab (Table 3), which act in different ways to inhibit osteoclast activity [72], maintaining trabecular structure and increasing bone mass. Bisphosphonate treatment duration ranged from 12 to 49 months. Seven studies reported a preservation of TBS with bisphosphonates, SERMs and MHT [19, 22, 23, 57, 60, 62, 63] and three reported small, significant gains ranging from 0.7 to 1.4% over 12 months [57, 59, 71]. Seven

Table 2 Treatment-related changes in lumbar spine trabecular bone score (TBS)

First author, year	Location	Design	Duration (m)	Subjects	TBS software version	%TBS change from baseline	%LS BMD change from baseline
Antiresorptive treatments							
Shin 2017 [59]	South Korea	Prospective	23	209 PM women on bisphosphonates (alendronate, risedronate or ibandronate)	2.0	2.69%*	9.3%*
McClung 2017 [20]	Multi-national	RCT	36	157 PM women on denosumab 128 PM women on placebo	1.9	2.4%** − 0.7%	9.8%** 0%
Leslie 2017 [19]	Canada	RCT	49	1884 women on bisphosphonates 3961 untreated	2.1	0.8% − 1.2%	6.3%* − 1.7%
Sooragonda 2019 [58]	India	Prospective	24	90 PM women on zoledronate	3.0	− 1.4%	6.1%*
Miyaoka 2020 [61]	Japan	Prospective	12	19 PM women on denosumab 19 PM women post-PTX surgery	NR	3%* 2.8%	6%** 11.2%**
Kim 2022 [62]	South Korea	Open-label	12	49 PM women with T2D on ibandronate 55 PM women on ibandronate	NR	NS (v NR) NS	3.7%* 3.4%*
Hans 2022 [70]	Multi-national	RCT	36	150 PM women on denosumab 129 untreated	3.0 & 4.0	3.3%* (TBS _{TTh}) − 1.4%	10.5%** 0%
Hans 2023 [24]	Multi-national	RCT	120	150 PM women on long-term denosumab 129 PM women untreated (36 m) to denosumab (120 m)	4.0	4.7%** (TBS _{TTh}) 3.2%**	22.4%** 17.2%**

Table 2 (continued)

First author, year	Location	Design	Duration (m)	Subjects	TBS software version	%TBS change from baseline	%LS BMD change from baseline
Leslie 2023 [69] ^a	Canada	Prospective	38	6,985 women and men (6%) (mean age 65 y) on antiresorptives (78% bisphosphonates, 22% SERMs or MHT) <i>Results reported at individual level (LSC)</i>	3.0	Increase = 9.3% No change = 76.9% Decrease = 13.8%	Increase = 22.0% No change = 61.9% Decrease = 16.1%
Anabolic treatments							
Cipriani 2018 [65]	USA	Prospective	18	19 PRE women on rhPTH(1–84) 38 PM women on rhPTH(1–84) 16 PM women (hypoparathyroid) on rhPTH(1–84)	2.1	3%* 0% 1.3%	3%* 6.2%* 3.1%*
Bilezikian 2018 [66]	Multi-national	RCT	6	29 PM women on 20ug abaloparatide 25 PM women on 40ug abaloparatide 24 PM women on 80ug abaloparatide 31 PM women on 20ug teriparatide 29 untreated	4.0	2.3%** (TBS _{TtH}) 3.1%** 4.2%** 2.2%** – 1.1%	NR
Sandeep 2022 [68]	India	Prospective	24	51 PM high-risk OP women on teriparatide	3.0	9.6%**	7.3%**
Chen 2022 [67]	Taiwan	Prospective	12	121 PM women on teriparatide	3.0	3%*	9%**
Treatment comparisons or sequential treatment							

Table 2 (continued)

First author, year	Location	Design	Duration (m)	Subjects	TBS software version	%TBS change from baseline	%LS BMD change from baseline
Di Gregorio 2015 [57]	Spain	Open-label	24	67 untreated	2.1	-3.3%*	0.5%
				87 PM women and men on calcium and vitamin D		NS	NS
				88 PM women and men on alendronate		1.4%*	4.1%*
				39 PM women and men on risedronate		NS	4.8%*
				43 PM women and men on denosumab		2.8%*	8.8%**
				30 PM women and men on teriparatide		3.6%*	8.8%**
				25 PM women on teriparatide to denosumab			
Tsai 2017 [21]	USA	Open-label	48	22 PM women on denosumab to teriparatide	2.2	2.7%** (24 m)	9.5%** (24 m)
				18 PM women on combined to denosumab		5.1%** (48 m)	18.3%** (48 m)
				25 PM women on teriparatide to denosumab		1.8%* (24 m)	8.3%* (24 m)
				18 PM women on combined to denosumab		3.6%** (48 m)	14%** (48 m)
				22 PM women on denosumab to teriparatide		4.5%* (24 m)	12.9%* (24 m)
Miyaoaka 2017 [61]	Japan	Controlled trial	12 & 24	28 PM women and men on teriparatide (12 m)	NR	4.8%*	10.3%*
				19 to minodronate (to 24 m)		+0.2%	(+0.5%)
Jeong 2021 [22]	South Korea	Prospective	12	10 PM women on romosozumab	3.0	2.5%*	8.3%*
				21 PM women on denosumab		0.6%	6.5%*
				24 PM women on ibandronate		-0.5%	3.3%*
Kang 2022 [63]	South Korea	Prospective	24	188 PM women on denosumab	2.2	2.5%**	9.7%**
				183 PM women on zoledronic acid		0.1%	6%**

Table 2 (continued)

First author, year	Location	Design	Duration (m)	Subjects	TBS software version	%TBS change from baseline	%LS BMD change from baseline
Cosman 2023 [23]	Multi-national	RCT	43	457 PM women on abaloparatide (18 m) to alendronate 454 untreated (18 m) to alendronate	3.0 & 4.0	4% ^{**} (18 m), 4.4% (43 m) (TBS _{TTh}) NS (18 m), 1.7% (43 m)	NR
McClung 2022 [71]	Multi-national	RCT	12 and 36	190 PM women on romosozumab (12 m) to alendronate 188 PM women on alendronate (36 m)	4.0	5.1% ^{**} (12 m); 4.8% [*] (36 m) (TBS _{TTh}) 1.5% (12 m); 2.5% [*] (36 m)	NR

BMD, bone mineral density, PM, postmenopausal, NR, not reported, NS, not significant, RCT, randomized controlled trial, T2D, type 2 diabetes, rhPTH, recombinant human parathyroid hormone; TBS_{TTh}, TBS using the updated software (v4) taking into account tissue thickness (studies reported similar significant findings with the currently available TBS software accounting for BMI but in lesser amplitude). * $p < 0.05$, ** $p < 0.005$ compared to baseline.

^a Study did not report mean %change in TBS or BMD. Results expressed as % exceeding or not exceeding least significant change (LSC).

reported significant gains in BMD, ranging from 1.5 to 4.9% over 12 months [19, 22, 57, 59, 60, 62, 63].

One recent study examined changes based on least significant change (LSC) in 6,985 adults (mean age 65 y, 94% women) treated primarily with bisphosphonates (78.3%), followed by SERMs (12%) then MHT (6.2%), over a mean treatment period of 38 months [69]. Consistent with findings from studies reporting on group mean treatment effects [18, 22, 57, 59–62], the proportion of individuals with an increase in lumbar spine BMD (22%) and hip BMD (17.6%) was greater than those who had an increase in TBS (9.3%). The treatment effect on TBS was primarily one of preservation which aligns with the mechanisms of action (TBS: 76.9% within LSC, Table 2) [69, 72]; indeed an increase in TBS would not necessarily be expected with antiresorptive treatment. An increase in TBS greater than the LSC should occasion consideration of potential technical factors, such as change in body weight, tissue thickness or scan mode, all of which also impact changes in BMD though to a somewhat lesser extent [69]. It is noteworthy that in the same study, 24.9% and 16.1% of patients had a decrease in hip and spine BMD which exceed LSC, which might also necessitate an investigation of clinical issues such as compliance or technical issues such as scan mode, weight change and DXA instrument.

Denosumab treatment durations ranged from 20 months to 10 years (Table 3). All studies reported significant increases in TBS with denosumab treatment, ranging from 0.4 to 1.8% /12 months, and increases in BMD ranging from 1.9 to 6%/12 months. One study included a comparison of TBS software versions for monitoring treatment with denosumab over 36 months [70]. Denosumab led to progressive increases in BMD and TBS over 36 months, with both TBS (version 3, BMI-adjusted) and TBS (version 4.0, tissue thickness adjusted) changes being significant compared to baseline and compared to placebo, from months 12 to 36 ($p < 0.001$). The mean percent changes from baseline with TBS version 3.0 were 1.4%, 1.5% and 1.9%, at months 12, 24, and 36 respectively, while for TBS (version 4.0), the mean increases were slightly better at 2.3%, 2.6% and 3.3%, respectively [70]. In a further study, the efficacy of long-term denosumab therapy was investigated in 279 postmenopausal women who were randomized to either long-term denosumab treatment for 10 years or placebo for 36 months followed by denosumab for 7 years [24]. Consistent increases in TBS to 4.7% and in BMD to 22.4% were observed in women on long-term denosumab treatment. For women in the cross-over denosumab group, there were significant increases in TBS to 3.2% for seven years following treatment initiation, and in BMD, to 17.2%. At the individual level, denosumab treatment over 10 years resulted in a reduction in the proportion of women with degraded TBS (from 48.6 to 29.1%) and an increase in the proportion of

Table 3 Secondary osteoporosis treatment-related changes in lumbar spine trabecular bone score

First author, year	Location	Design	Duration (m)	Subjects	%TBS change from baseline	%LS BMD change from baseline
Aromatase inhibitors						
Pedrozzoni 2014 [144]	Italy	Retrospective	36	29 early PM women, no MHT (mean age 51 y) 34 women treated with aromatase inhibitors (mean age 54 y)	−4.6%* −2.1%*	−6.8%* −5.9%*
Marlotti 2016 [145]	USA	Prospective	21	100 women with breast cancer treated with aromatase inhibitors (mean age 67 y)	−1.0%*	−3%*
Hong 2017 [144]	South Korea	Prospective	48	321 PM women with breast cancer treated with aromatase inhibitors	−2.1%*	−6.2%*
Catalano 2019 [147]	Italy	Prospective	18	60 women with breast cancer treated with aromatase inhibitors 42 controls	−2.2%* −0.4%	−2.9%* −0.7%
Glucocorticoids and methotrexate						
Chuang 2017 [152]	Taiwan	Controlled trial	24	30 PM women treated with glucocorticoids 16 PM women no treatment	−5.9%* 0.6%	−3.4%* −0.7%
Killinger 2019 [155]	Slovakia	Prospective	12	21 men and women with rheumatoid arthritis on methotrexate 81 men and women with rheumatoid arthritis on biologic-disease modifying drugs (mean age 54 y)	0% 1.7%*	−0.3% 0%
Corrado 2021 [153]	Italy	Prospective	12	22 men and women on high-dose glucocorticoids 25 men and women on low-dose glucocorticoids (mean age 38 y)	−10%* −1.7%*	−18%* −12%*
Rymuza 2022 [154]	Poland	Pilot trial	4	15 men and women on glucocorticoids (mean age 54 y)	−2.4%*	1.6%*
Other treatments associated with secondary osteoporosis						
Ock 2016 [156]	Korea	Prospective	21	30 men and women with Grave's disease treated by TSH suppression therapy (mean age 35 y)	1%*	4%*
Godang 2016 [157]	Norway	Prospective	120	48 men and women with acromegaly treated with somatostatin therapy or post-pituitary surgery (mean age 48 y)	−3%*	3.2%*
Toussiro 2017 [158]	France	Prospective	24	8 men and women with rheumatoid arthritis on anti-TNFα 12 men and women with ankylosing spondylitis on anti-TNFα	−3.9%* NS	3.2%* 6.2%*

Table 3 (continued)

First author, year	Location	Design	Duration (m)	Subjects	%TBS change from baseline	%LS BMD change from baseline
Nordkling 2018 [159]	Denmark	RCT	18	185 men and women T2D treated with metformin 180 men and women T2D on placebo (age \geq 65 y)	−3.6%* −4%*	NS NS
Chung 2021 [160]	Korea	Prospective	48	410 PM women with differentiated thyroid carcinoma, post-thyroidectomy and with TSH suppression	−6%*	−4%*
Guan 2021 [91]	China	Prospective	10	233 men and women with HIV infection treated with anti-retroviral therapy (mean age 37 y)	−1.6%*	−3%*
Lee 2021 [108]	Korea	Case-control	12	100 men and women T2D on dipeptidyl peptidase-4 inhibitor 100 T2D controls (mean age 68 y)	1.2%* −1.1%*	NS NS
Yokomoto-Umakoshi 2021 [161]	Japan	Prospective	12	18 men and women with surgical resection of paraganglioma	2.4%*	NR
Antiestrogen treatments – antiresorptives						
Librizzi 2016 [162]	Spain	Prospective open-label	12	89 men and women post liver transplant randomized to risedronate or untreated (mean age 58 y)	NS	4.8%*
Maria 2016 [163]	Spain	Prospective	60	70 PM women on aromatase inhibitors, treated with bisphosphonates 200 PM women on aromatase inhibitors without bisphosphonates	2%* −3%*	5%* −2%*
Prasad 2016 [164]	USA	RCT	24	109 women with breast cancer on aromatase inhibitors, with risedronate or without risedronate (mean age 71 y)	−1.2% −2.4%*	2.3%* −1.7%*
Bonani 2019 [165]	Switzerland	Prospective	12	44 kidney transplant patients on denosumab Untreated controls (mean age 51 y)	4%* 1.5%	3.7%* 0.1%
Cauley 2021 [166]	USA	RCT	12	105 hypogonadal men on testosterone therapy 92 hypogonadal men placebo (mean age 72 y)	1.6% 1.4%	6%* 0.4%
Kim 2022 [62]	South Korea	Open-label	12	49 PM women T2D on ibandronate 55 PM women non-T2D on ibandronate	NS NS	3.7%* 3.4%*
Antiestrogen treatments – anabolic, comparing therapies or sequential treatment						
Saag 2016 [167]	USA	RCT	36	53 PM glucocorticoid-treated women on alendronate 56 PM glucocorticoid-treated women on teriparatide	NS 3.7%*	5.5%* 10.3%*

Table 3 (continued)

First author, year	Location	Design	Duration (m)	Subjects	%TBS change from baseline	%LS BMD change from baseline
Cipriani 2017 [65]	Italy	Prospective	24	52 men and women with hypoparathyroidism, on rhPTH(1.84) 27 men and women PHPTH post-parathyroidectomy	1%* NS	3%* 3%*
Dhaliwal 2020 [168]	USA	RCT	18	65 PM women T2D on abaloparatide 80ug 68 PM women T2D on teriparatide 20ug 65 PM women T2D placebo	3.7%* 2.4%* 0.6%	8.9%* 2.7%* 1.3%
Shane 2021 [169]	USA	Extension trial	48	32 premenopausal women with idiopathic osteoporosis on teriparatide (24 m) to denosumab (29 completed to 48 m)	5.8%*	21.9%*
Munekawa 2022 [170]	Japan	Retrospective cohort	12	26 PM women T2D on bisphosphonates 12 PM women T2D on teriparatide 52 untreated (mean age 73y)	NS NS NS	5.5%* 4.1%* 1.1%*

BMD, bone mineral density; *PM*, postmenopausal; *PHPTH*, primary hyperparathyroidism; *RCT*, randomized controlled trial; *TSH*, thyroid stimulating hormone; *T2D*, type 2 diabetes; * $p < 0.05$.

women with normal TBS (26.1 to 53.2%). Similarly, there was a reduction in the proportion of women classified at high risk of fracture according to the combination of TBS and BMD T-score (from 94 to 40%) [24]. Furthermore, consistent with TBS as a predictor of fracture, women with the greatest improvements in TBS experienced fewer new fractures or worsening fractures across the trial duration [24].

Collectively, the evidence indicates that bisphosphonates, SERMs and MHT are unlikely to result in TBS change as they act primarily to preserve bone microarchitecture, as confirmed by histomorphometric analyses [72, 73]. On the other hand, denosumab, a more potent antiresorptive agent [72, 74] with a potential bone-forming effect [74], results in sustained, modest to large gains in TBS with extended treatment durations up to 10 years [24].

Anabolic agents

Anabolic treatments studied included parathyroid hormone (PTH) analogues which act by increasing bone formation and resorption, and romosozumab, which through a novel, dual mode of action, rapidly increases bone formation and reduces bone resorption [75]. In histomorphometric analyses, both

classes of treatment have been shown to significantly improve trabecular microarchitecture and bone volume [76, 77]. Eight studies included PTH/PTHrP analogues (teriparatide and/or abaloparatide) and demonstrated mean increases in TBS from 1.3 to 4.8%/12 months and increases in BMD ranged from 2.0 to 8.3%/12 months (Table 2).

In a multi-national randomized controlled trial (RCT), 109 postmenopausal women (mean age 61.5 y) received abaloparatide (20, 60 or 80ug) or 20 ug teriparatide over 6 months [66]. Rapid increases in TBS were observed in all treatment groups, with the greatest increases observed with the higher 80ug dose of abaloparatide (4.2%). At the individual level, 52% of women on abaloparatide (80ug) and 30% of women on teriparatide, had a TBS increase which exceeded LSC. With a longer intervention duration, the ACTIVE and ACTIVEExtend RCT demonstrated a mean TBS increase of 4% over 18 months in 457 postmenopausal women treated with abaloparatide [23]. This increase was sustained to 4.4% at 43 months, and 50% of women had a positive change which exceeded LSC. There was also a reduction in the proportion of women with degraded TBS (from 40 to 24%) while there was no change in the TBS category for women in the placebo group (from 43 to 45%). In the same trial, compared to those not having an increase in

TBS greater than LSC (3.8%), the odds ratio of sustaining a new vertebral fracture over 43 months was lower in those with a greater than LSC increase at 6 months (OR: 0.19, 95%CI 0.04, 0.8) and at 43 months (OR: 0.3, 95% CI 0.11, 0.79) [23].

Romosozumab rapidly increased lumbar spine and hip BMD with an effect size greater than that observed with PTH/PTHrP analogues [76]. Treatment with romosozumab results in significant reductions in vertebral fracture and MOF risk [77] and medication has been recommended as the first line of treatment in patients with very high fracture risk [78, 79]. Two studies have investigated the effect of romosozumab on TBS [22, 71]. The first, in a small sample of 10 women (mean age 66 y), demonstrated a 2.5% mean increase in TBS and an 8.3% increase in lumbar spine BMD with 6 months of romosozumab treatment [22]. Conversely, in this study, there were no changes in TBS following 12 months of antiresorptive treatment [22]. In the ARCH multi-centre RCT, TBS measurements were available in 378 women (mean age 73 y, ~9.3% of the study population) randomized to receive either romosozumab or alendronate [71]. Over 12 months, mean TBS increased significantly by 5.1% in women treated with romosozumab, compared to no significant change (mean + 1.5%) in those treated with alendronate [69]. Furthermore, treatment with romosozumab led to a reduction in the proportion of women with degraded TBS (from 52.6 to 33%) and an increase in the proportion of women with normal TBS (28.9 to 48.1%). In women treated with alendronate only, there was a smaller reduction in the proportion of those with degraded TBS (from 60.6 to 51.6%) and a smaller increase in those with normal TBS (from 26.1 to 33%) [71].

Sequential osteoporosis treatment regimens

The long-term management of osteoporosis, particularly in patients at very high fracture risk, may necessitate sequential treatment [79]. Recent recommendations suggest that this may require an anabolic-first treatment regimen with a bone-forming agent (such as romosozumab or PTH, PTH/PTHrP-analogue) for 1–2 years, followed by an antiresorptive (such as a bisphosphonate or denosumab) for a further 5–10 years [80]. In the DATA-Switch open-label trial, postmenopausal women were allocated to sequential treatment comprising teriparatide to denosumab, or denosumab to teriparatide [21]. After 24 months, TBS gains were greater in the anabolic first group (2.7% versus 1.8%), and continued to increase for a further 24 months, following the treatment switch (5.1% versus 3.6%). In the ARCH multi-center trial, the 5.1% increase in TBS with romosozumab at 12 months was maintained to 4.8% with alendronate, for a

further 24 months [71]. In a comparison group of women treated only with alendronate, gains in TBS were lower (1.5% at 12 months, 2.5% at 36 months). This approach may also be useful in patients whose very high risk of fracture is driven by reduced bone density and/or degraded bone microarchitecture.

TBS and treatment decision-making

The initiation of treatment is increasingly driven by fracture risk, which may be assessed by a variety of risk assessment modalities, depending on the availability of densitometry and FRAX, and on country or regional-specific guidance. European guidelines recommend FRAX-based approaches [81, 82] with age-dependent intervention thresholds [83]. The adjustment of FRAX for TBS provides a global risk assessment based on bone mass and bone microarchitecture, plus clinical risk factors. Alternatively, the adjustment of the lowest BMD for TBS captures fracture risk associated with reduced bone mass and degraded bone microarchitecture, and the adjusted T-score may be entered into fracture risk calculators, such as the Garvan fracture risk calculator [84]. At the conceptual level, the information that TBS conveys regarding bone microarchitecture suggests that this measure, taken with BMD and CRFs, might contribute to decisions about specific treatment strategies. For example, on this basis, a treatment regimen might be chosen to either increase BMD and preserve bone microarchitecture, or to increase both BMD and bone microarchitecture, with consolidation thereafter. While a conceptually appealing mechanism by which treatment could be chosen according to individual patient characteristics, it clearly requires further evidential underpinning in order to properly inform this suggested approach.

As with BMD, the monitoring of treatment effect at the individual level should apply LSC based on centre-specific precision error and acquired in accordance with ISCD guidelines [85]. Few studies to date have reported on the proportion of study participants exceeding TBS or BMD LSC [19, 20, 23, 66], and it is recommended that future studies include this data to enable interpretation of treatment effect at the individual level. Precision errors for TBS using Hologic or GE DXA systems and different TBS software versions, are comparable to BMD precision [84] and have ranged from 0.8 to 2.1%CV with equivalent LSC ranging from 2.2 to 5.8%. The average precision error and LSC from studies to date are 1.4%CV and 3.8% respectively [9, 36, 40, 63, 68, 86–91]. The corresponding LSC unit change in TBS has been reported to be 0.05 based on a precision of 1.4%CV [85].

Statements (GRADE outcome: strongly recommended)

The expert Working Group members made the general recommendation that TBS results should be interpreted within the clinical context of the patient. Individual statements, all of which were strongly supported by the members of the Working Group, are itemized below:

7. Patients with low TBS who lie below but near the treatment threshold should be considered for an earlier assessment and lifestyle advice.
8. TBS with BMD and FRAX probability contributes to the stratification of antiosteoporosis therapy according to fracture risk, directing very high-risk patients to anabolic-first approaches.
9. TBS in conjunction with BMD, is useful for monitoring individual response to long-term denosumab treatment (5 years or more).
10. TBS in conjunction with BMD is useful for monitoring individual response to PTH/PTHrP-analogue treatments such as teriparatide and abaloparatide.
11. TBS in conjunction with BMD is useful for monitoring the individual response to romosozumab.
12. A decrease in TBS more than LSC during treatment should prompt further clinical review.
13. TBS contributes useful information in the assessment of treatment response for patients receiving bone-forming agents or long-term denosumab.

Topic 3: Use of TBS in the prediction of fracture risk associated with secondary osteoporosis

Consistent with the growing clinical and research interest in this area, in 2015, four studies with fracture outcomes in secondary osteoporosis were reviewed [15], whereas, in the current review, 40 studies (seven prospective) met the eligibility criteria (prospective, retrospective or cross-sectional studies, fracture as the primary outcome, in men and/or women aged ≥ 18 years). Of these, three were conducted in Australia, one in Brazil, four in Canada, sixteen in Europe, two in India, three in Japan, four in South East Asia, seven in South Korea; 27 studies included men and 36 included women. Incident fragility fracture rates ranged from 8 to 31% and for prevalent fracture, from 10 to 45% (Table Sb, supplementary information). As would be expected, studies were often smaller, and more frequently cross-sectional rather than prospective, compared with those of TBS in the context of primary osteoporosis and risk assessment.

Type 2 diabetes

Type 2 diabetes (T2D) is associated with an increased risk of bone fragility and fractures, although the underlying mechanisms are not fully understood. Individuals with T2D have a higher risk of fractures despite in some cases, having higher BMD than non-diabetic individuals. This paradoxical relationship between BMD and fracture risk suggests that other factors, such as impaired bone quality (for example greater heterogeneity of trabecular bone microarchitecture and increased cortical porosity) and altered material properties (as a consequence of protein glycation), may be implicated [92–95]. Indeed, previous studies have suggested that the altered trabecular microarchitecture is at least in part due to the accumulation of advanced glycation end products in bone tissue which increases the propensity to fracture [96, 97]. Accordingly, the risk appears to be greater in patients who have poorer glycemic control [94, 95, 98]. In the current review, eight studies with cohort sizes between 169 and 44,503, investigated the use of TBS for the prediction of fragility fracture in T2D patients (Table Sb, supplementary information). In seven studies, TBS was related to fragility fracture risk independent of BMD [16–18, 99–101, 103] and three reported enhanced fracture risk prediction with TBS-adjusted FRAX compared to FRAX alone [16, 99, 100]. In 44,543 men and women (mean age 63.9 y) from the Manitoba cohort, 3,946 (9%) sustained an incident MOF over a mean follow-up of 8.3 years [99]. Individuals with T2D ($n = 4136$) had significantly lower TBS but higher femoral neck BMD ($p < 0.05$). Diabetes was also a significant predictor of incident fragility fracture risk, supporting findings from earlier studies in both sexes [94, 95] and of microarchitectural deterioration in T2D-related skeletal fragility [100]. The adjustment of FRAX for TBS in the diabetes sub-group resulted in an overall NRI of 3.9% for incident MOF and 2.5% for hip fracture. Most reclassification was upward, based on a fixed intervention threshold of 20% for MOF and 3% for hip fracture [100].

Hypercortisolism and glucocorticoid-induced fracture risk

Six cross-sectional studies examined associations between TBS and prevalent or recent fragility fracture in patients with Cushing's syndrome [104] or treated with corticosteroids [105–109]. All reported that TBS was associated with fracture, independent of BMD. In 182 men and women with Cushing's syndrome (mean age 37.8 y; 45% fractured), there were no associations between BMD and

fracture [104]. However, 84% of fractured patients had either degraded (50%) or partially degraded (34%) TBS (compared to 40% with low BMD), suggesting an important role for TBS-detected parameters including degraded trabecular architecture in the elevated fracture risk associated with endogenous overproduction of cortisol [104]. Comparable skeletal profiles have also been observed in patients receiving long-term corticosteroid treatment [108, 109]. In 127 Spanish patients treated with corticosteroids (mean duration, 47.7 months), 27% had sustained a recent fragility fracture [108]. The skeletal profiles of patients with vertebral or non-vertebral fragility fracture were predominantly characterized by degraded TBS (76% and 69% respectively) rather than densitometric osteoporosis (38% and 36% respectively).

Chronic kidney disease

Seven studies met the inclusion criteria and investigated the use of TBS for predicting fracture in patients with chronic kidney disease (CKD) [110–116]. Five studies showed that TBS predicted incidents or were associated with a prevalent fragility fracture, independent of BMD [110–114]. Whilst CKD metabolic bone disease represents several different histomorphometric phenotypes, the search did not identify studies specifically addressing this point. In 1426 men and women (mean age 67 y), reduced kidney function was associated with significantly lower TBS and a higher probability of fracture (18% vs. 6%, $p=0.01$) and low TBS predicted greater incidence of fragility fractures over 4.7 years, independent of BMD and CRFs [110]. Lower TBS also corresponds with increasing disease severity [111, 112]. In hemodialysis patients (mean age 74 y), TBS and not BMD, was a significant, independent predictor of fracture [115]. Two studies did not report an association between TBS and fracture risk in CKD patients. First, a retrospective cohort study, found that neither TBS nor BMD were related to a history of fracture in men with moderate CKD (age 33 to 96 y) [113]. Second, in a prospective study of a modest sample of 59 CKD patients (mean age 68 y), FRAX-adjusted for TBS was higher in fracture compared to non-fracture cases (16.8% versus 10.6%), but the predictive model did not reach statistical significance [112].

Rheumatological conditions

Ten studies investigated TBS for fracture prediction/discrimination in rheumatological inflammatory conditions including rheumatoid arthritis [118–120], axial spondyloarthritis [121], ankylosing spondylitis [122–124], poly-myalgia rheumatica [125], systemic lupus erythematosus

[126] and systemic sclerosis [127]. The risk factors for skeletal fragility in these conditions include inflammatory disease mechanisms and cytokine-activation of bone resorption, in addition to the use of glucocorticoid and other immunosuppressive drugs, which are known to affect bone microarchitecture [128]. All studies showed that TBS was significantly associated with fracture, independent of BMD. In two studies of postmenopausal women with rheumatoid arthritis, TBS but not BMD was associated with a prevalent radiographic vertebral fracture [118, 119], and adjustment of FRAX for TBS improved fracture risk prediction compared to FRAX alone [119]. In a separate study of 142 rheumatoid arthritis patients and 106 healthy controls, lower TBS was associated with vertebral fracture and of those with vertebral fracture, 26% had normal lumbar spine BMD and 12% had normal hip BMD [120].

Axial spondyloarthritis and ankylosing spondylitis are chronic inflammatory conditions that can lead to structural damage to bone tissue, degraded bone microarchitecture and increased fracture risk [129]. In all four studies reviewed, TBS was significantly associated with past or incident fracture [121–124], and in two studies femoral neck BMD, but not lumbar spine BMD, was lower in fracture cases [122, 124]. In patients with axial spondylitis, those with fractures were more likely to have degraded TBS (29%) than low BMD (14%) [121]. It is also important to consider that lumbar spine BMD can be falsely elevated in degenerative noninflammatory arthropathy (due to sclerosis and osteophytes) and in certain inflammatory rheumatic diseases including ankylosing spondylitis (resulting from syndesmophyte formation). In a recent study of 63 spinal surgery patients, lumbar spine BMD was significantly increased with higher CT-derived degeneration scores ($p < 0.001$) whereas TBS and CT Hounsfield unit measurements were unaffected [130]. In the case of a patient who may have degraded TBS and normal or increased lumbar spine BMD, careful scrutiny of the DXA image is recommended to ensure that no vertebrae are affected by spinal artefacts.

Other causes of secondary osteoporosis

Ten studies investigated other causes of secondary osteoporosis including acromegaly, cirrhosis, hyperparathyroidism, pulmonary disease, HIV infection, and thalassemia [131–140]. These studies tended to be small and cross-sectional in nature. In one study of 106 men and women with acromegaly (mean age 56 y), despite lower TBS in vertebral fracture cases (1.18 vs. 1.202, $p < 0.05$), TBS was not associated with prevalent vertebral fractures in a multivariate model [134]. In the other

nine studies, TBS was associated with prevalent vertebral fractures, independent of BMD [131–133, 135, 137–140] or enhanced fracture prediction when combined with BMD [136]. In four of these studies, however, BMD did not differ between fracture and non-fracture cases [131, 133, 135, 139].

Five studies examined TBS and hyperparathyroidism or hypoparathyroidism; conditions which are known to lead to alterations to trabecular bone microarchitecture [141, 142]. In studies of patients with hyperparathyroidism or hypoparathyroidism, TBS was significantly lower in fracture compared to non-fracture cases [132, 135, 137, 139, 140]. In studies that examined the skeletal profiles of fracture cases, the prevalence of degraded TBS (35 to 57%) was greater than densitometric osteopenia or osteoporosis (11 to 21%) [137, 139]. Similar skeletal profiles indicating a predominance of altered bone microarchitecture were also reported in chronic obstructive pulmonary disease [135] and thalassemia [136]. In patients with thalassemia, more fractured patients had degraded TBS (57%) than low BMD (20%) [136].

Statements (GRADE outcome: strongly recommended)

14. Reductions in TBS are observed in most secondary osteoporosis-related diseases.
15. TBS predicts fracture risk in type 2 diabetes, independently of BMD and FRAX probability.
16. TBS predicts fracture risk in chronic kidney disease, independently of BMD.
17. TBS predicts fracture risk in patients treated with glucocorticoid, independently of BMD.
18. TBS predicts fracture risk in rheumatological diseases, for example, rheumatoid arthritis, independently of BMD.
19. TBS is relatively unaffected by spinal changes such as osteophytes and syndesmophytes.

Topic 4: Use of TBS for treatment monitoring in secondary osteoporosis

Twenty-eight studies met the eligibility criteria (prospective, retrospective cohort or case–control cross-sectional design; treatments associated with secondary causes of osteoporosis, or antiosteoporosis therapies in secondary osteoporosis; men and/or women, age ≥ 18 years) and thirteen studies included men (Table 3). One study was conducted in China, one in Denmark, one in France, four in Italy, two in Japan, five in Korea, one in Norway, one in Poland, one in Slovakia, two in Spain, two in Switzerland, one in Taiwan and six in the USA. Fourteen studies investigated the effects of treatments associated with secondary osteoporosis, and fourteen investigated the efficacy of antiosteoporosis therapies (Table 3).

Aromatase inhibitors

Aromatase inhibitors (AI) are first-line therapies for reducing the risk of cancer recurrence in postmenopausal women with hormone-receptor-positive breast cancer, by inhibiting the conversion of androgens to estrogen. Given this mechanism of action, AI therapies accelerate bone turnover, increase bone resorption, reduce bone density and increase fragility fracture risk [143]. Four studies investigated the effect of AI therapy (duration from 18 to 48 months) on TBS in postmenopausal or early postmenopausal women with breast cancer [144–147]. Reductions in TBS ranged from -0.5 to -1.5% /12 months, with the greatest loss observed over 36 months (-4.6%), unrelated to change in BMD [145]. In a retrospective, longitudinal study of 321 non-osteoporotic postmenopausal women with breast cancer (mean age 59 y), AI treatment for 3 years, negatively affected both BMD and TBS [147]. BMD significantly decreased by 6.1% and TBS by 2.1%, independent of BMD. The loss of TBS was more pronounced during the first year of treatment with a slowing thereafter, whereas the annual loss of BMD continued for up to 4 years.

Glucocorticoids

Prolonged use of glucocorticoids increases fracture risk [148]. Previous studies have demonstrated that glucocorticoids can weaken bone microarchitecture, for example, through a major loss of trabecular connectivity [149, 150], with disease mechanisms involving increased osteoclastogenesis and apoptosis of osteoblasts and osteocytes [151]. Three studies investigated the effect of glucocorticoid treatment on TBS, and all reported significant reductions ranging from -3 to -10% /12 months, with decreases in BMD ranging from -1.7 to 18% /12 months [152–154]. The largest reduction in TBS was reported in men and women (mean age 38 y) with rheumatoid arthritis, treated with high-dose compared to low-dose glucocorticoids over 12 months (-10% vs. -1.7%) indicating that the magnitude of the effect is dependent on treatment dose regimen [153].

Antiosteoporosis treatments in patients with secondary osteoporosis

Ten studies investigated the effects of antiresorptive treatments and five examined anabolic treatments. Of these studies, five included men. Collectively, the effects of treatment on TBS and BMD (Table 3), were comparable to those observed in postmenopausal osteoporosis (Table 2), reflecting the drug mechanisms of action and duration of treatment.

Antiresorptive agents included bisphosphonates, denosumab and testosterone therapy. One placebo-controlled

RCT examined the effect of 12 months testosterone therapy in 197 androgen-deficient men (mean age 54 y) [166]. No significant differences in TBS were reported between the treatment and placebo groups (1.6% vs. 1.4%), although a significant effect on QCT-derived BMD was observed. In studies of bisphosphonates, the treatment effect, as in postmenopausal women, was one of preservation with no significant changes in either direction reported [62, 162–164, 167]. One RCT over 24 months included 109 women with breast cancer and treated with AI, who received either 35 mg/week risedronate or a placebo [164]. A significant loss of TBS (−2.4%) and BMD (−1.7%) was demonstrated in women receiving the placebo, whereas in women treated with risedronate, there was no change in TBS and an increase in BMD (2.3%). Similar findings were reported in osteopenic/osteoporotic men and women with liver cirrhosis [162], in women with T2D [168, 169], and in corticosteroid-treated women [167]. On the other hand, TBS significantly increased by 4% in CKD patients treated with denosumab over 12 months [165].

Studies of anabolic agents included PTH/PTHrP analogues [62, 65, 168–170] and one extension RCT investigated the effects of a sequential anabolic-first treatment regimen [169]. Overall, anabolic treatments led to increases in TBS ranging from 0.5 to 2.5%/12 months. In the largest RCT and part of the ACTIVE trial, 198 postmenopausal osteoporotic women with T2D received either 80ug abaloparatide, 20ug teriparatide or placebo over 18 months [168]. The largest increases in TBS and BMD were observed in the abaloparatide group (3.7% and 8.9% respectively) although gains with teriparatide were also significant (2.4% and 2.7% respectively). A separate RCT investigated the efficacy of teriparatide in glucocorticoid-treated women and reported significant increases in TBS of 3.7% and increases in BMD of 10.3% [167], whereas treatment with alendronate led to increases in BMD (5.5%) and no change in TBS. One study investigated sequential therapy in 32 premenopausal women (mean age 39 y) with severe idiopathic osteoporosis and a history of fragility fractures [169]. Teriparatide for 12 to 24 months, followed by 24 months of treatment with denosumab led to a sustained mean increase of 5.8% in TBS, comparable to findings in postmenopausal women [21].

Statements (GRADE outcome: strongly recommended)

20. TBS adds value when used with BMD in monitoring skeletal effects of aromatase inhibitors.
21. TBS adds value when used with BMD in monitoring skeletal effects of glucocorticoids.
22. Evidence supporting the use of TBS in monitoring response to antiosteoporosis therapy is applicable across both primary and secondary osteoporosis.

Ongoing developments and future research

Recent and ongoing developments in TBS software include the updated TBS algorithm (version 4) that accounts for soft tissue thickness, as an improvement on the current algorithm which estimates tissue thickness using body mass index as a surrogate (version 3.1.2). The updated algorithm has been shown to perform similarly to previous versions of TBS in the prediction of fragility fracture [41] and be equally or more effective when monitoring changes in TBS in response to antiresorptive and anabolic osteoporosis therapies [23, 24, 64, 70, 71]. Given the incorporation of soft tissue adjustment, there is further potential for application in pediatric populations [171], in patients undergoing significant weight change and in patients with very high or very low BMI [172], although further studies are required. There are also several recent studies that demonstrate the versatility and expansion of TBS to other skeletal regions including the hip [173], the distal femur following knee arthroplasty [174] and lateral vertebral fracture assessment [175]. Further research in these areas is encouraged.

Conclusions

Evidence supporting the added value of TBS in the assessment and management of osteoporosis has rapidly accumulated since 2015. Collectively, data indicate that TBS enhances fracture risk prediction in both primary and secondary osteoporosis, and across diverse races and ethnicities. Together with FRAX, the inclusion of TBS in conjunction with BMD can provide an improved global assessment of fracture risk, which takes into account the two pillars of fracture resistance (bone mass and bone microarchitecture) and CRFs. Where FRAX is not available, TBS alongside BMD provides a dual skeletal assessment of fracture risk, and the lowest BMD T-score-adjusted for TBS can be input into other fracture risk assessment tools. Limited data suggest that TBS is less influenced by degenerative and inflammatory spinal disease than DXA BMD. Furthermore, TBS has the potential to help inform treatment initiation and the choice of treatment in light of the overall skeletal profile of an individual patient, taking into account both BMD and bone microarchitecture. Including TBS in the monitoring of treatment may be useful for denosumab and anabolic agents, while with bisphosphonates, MHT and SERMs, evidence demonstrates that the effect is mostly one of preservation. The expert consensus statements and operational approach, provided in this paper, can be used to guide the integration of TBS in clinical practice for the assessment and management of osteoporosis.

Appendix 1. Operational considerations based on approved statements and expert opinion for the integration of TBS in clinical practice

Trabecular bone score (TBS) is grey scale texture measure that correlates with bone microarchitecture, which can be used alongside FRAX and BMD to enhance the assessment of fracture risk and to inform treatment initiation and monitoring. The following guidance can be used to facilitate the integration of TBS in clinical practice in alignment with clinical workflow (see Appendix Fig. 2).

Indications for the use of TBS (adapted from ISCD, 2019; Kanis et al., 2019)

- If FRAX (without BMD) indicates intermediate risk of fracture;
- In women aged 65 years or over, and men aged 70 years or over, for routine bone health monitoring;
- In women and men aged under 65 and 70 years respectively, TBS is recommended alongside BMD, if they have a risk factor for low bone mass such as low body weight, prior fracture, high-risk medication use, or a disease or condition associated with bone loss;
- Adults with a fragility fracture;
- Adults with a disease or condition associated with secondary osteoporosis;
- Adults taking a medication associated with secondary osteoporosis;
- Adults who are being considered for pharmacological treatment;
- Adults receiving treatment, to monitor treatment effectiveness;
- Adults not receiving osteoporosis treatment, when evidence of bone fragility would lead to treatment.

Image acquisition and quality assessment (technical considerations)

- A DXA scanner calibration with a dedicated fractal phantom is required for TBS software installations and when there is a change in the DXA system, in order to clinically interpret the data;
- When a DXA system is upgraded or replaced, it is strongly recommended that a new baseline TBS measurement is set for patients under treatment monitoring;
- Change in scan mode may impact TBS outcomes. This can be mitigated by ensuring correct measurement and data entry of height and weight, and avoidance of change in scan mode for longitudinal monitoring, unless indicated by the DXA manufacturer;
- Vertebrae affected by structural anomalies should be excluded from BMD analysis in accordance with ISCD protocol. Vertebrae excluded for BMD analysis are also excluded for TBS, e.g. sclerotic lesions, osteophytes, syndesmophytes, laminectomy and fracture;
- Spinal degenerative changes minimally impact TBS, unlike BMD. As such, it is not unusual to observe discordance between spine TBS (lower) and BMD (higher);

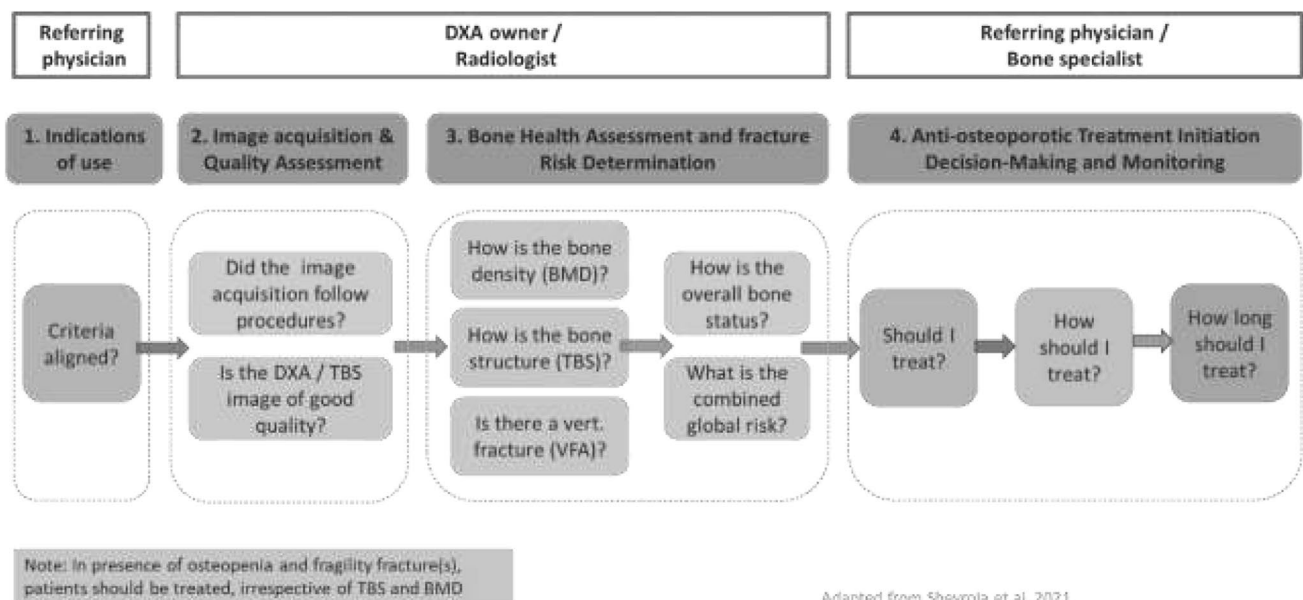


Fig. 2 Integration of TBS into the clinical workflow

- If two or more vertebrae are excluded, neither BMD nor TBS can be used for diagnosis;
- When a combination of vertebrae other than L1-L4 is used, combination-specific threshold adjustments are automatically applied in the current TBS iNsite version (3.1 and higher).
- The currently available TBS software is valid for use in individuals within the BMI range of 15 to 37 kg.m⁻². Interpretation of TBS results outside of this range should be made with caution.

Bone health assessment

- In the assessment of bone health, TBS can be used alongside BMD to provide additional information relating to bone microarchitecture;
- The ‘Bone Resilience Index’ is an interpretive tool provided by the manufacturer, comprising combinations of categories of BMD (normal, osteopenic or osteoporosis) and TBS (normal, partially degraded or degraded);
- Discordance between BMD and TBS (for example, normal BMD and degraded TBS), should prompt consideration of further clinical evaluation for possible causes of secondary osteoporosis;
- Vertebral fracture assessment (VFA) should be considered for osteopenic patients with degraded TBS.

Fracture risk assessment

- TBS can be used in the assessment of fracture risk using FRAX-adjusted for TBS directly OR indirectly by using the femoral neck BMD T-score-adjusted for TBS, but not both, to avoid over-adjustment for TBS;
- FRAX-adjusted for TBS can be used to adjust the probability of MOF or hip fracture, for bone microarchitecture, in men and women aged 40 to 90 years. The adjusted FRAX probabilities can then be compared to local or national intervention thresholds;
- In countries and regions where BMD T-score is the primary measure for assessment and reimbursement, BMD T-score-adjusted for TBS can be used;
- BMD T-score-adjusted for TBS can be used in fracture prediction models other than FRAX;
- The lowest adjusted T-score (lumbar spine, total hip or femoral neck) is used for diagnosis;
- Other approaches might include BMD Z-score (age 20 to 49 years) and the risk threshold adjustment (or treatment threshold shift) referring to the lowest BMD T-score adjusted for TBS Z-score;
- The selected approach should reflect patient age and country or region-specific guidelines.

Antiosteoporosis treatment initiation, decision-making and monitoring

- FRAX-adjusted for TBS or BMD T-score adjusted for TBS can be used to inform treatment initiation, in conjunction with country or region-specific treatment intervention thresholds;
- The greatest utility of either TBS adjustment is for individuals who are close to a FRAX or BMD T-score treatment intervention threshold;
- Patients with low TBS who lie below but near the treatment threshold should be considered for an earlier assessment and lifestyle advice;
- FRAX-adjusted for TBS can be used to guide the choice of anti-osteoporosis treatment in the framework of ESCEO-IOF recommendations on categorization to low, high or very high fracture risk (with the latter category directed to anabolic first regimens);
- Since TBS captures elements of bone microarchitecture, conceptually, a low (degraded or partially degraded) TBS might support the use of treatments that impact both BMD and bone microarchitecture, for example, long-term denosumab or bone anabolic agents;
- Conversely, bisphosphonates, SERMs and MHT might be considered if the treatment goal is preservation of TBS;
- Least significant change (LSC) should be used to interpret treatment effect at the individual level, based on the center-specific precision error;
- The average of published TBS precision errors and corresponding LSCs (Hologic and GE systems) are 1.37%CV and 3.79% respectively.
- If a patient has a significant reduction (exceeding LSC) in TBS during treatment, consider causes of secondary osteoporosis and if an alternative treatment is required;
- If a patient has a significant increase (exceeding LSC) in TBS and/or BMD during treatment while not expected given the given drugs and their associated mechanism of action, check for possible technical inaccuracies.

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Declarations

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