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Original article

Intervention thresholds to identify postmenopausal women with high fracture risk: A single center study based on the Philippines FRAX model

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A B S T R A C T

Objectives: This study is designed to estimate appropriate intervention thresholds for the Philippines Fracture Risk Assessment Tool (FRAX) model to identify postmenopausal women with high fracture risk.
Methods: Age dependent intervention thresholds were calculated for a woman of body mass index 25 kg/m^2 aged 50–80 years with a previous fragility fracture without other clinical risk factors. Fixed thresholds were developed using a database of 1546 postmenopausal women who underwent dual-energy X-ray absorptiometry for clinical reasons. Major and hip fracture risks were estimated using clinical risk factors with and without bone mineral density (BMD) input. Women were categorized to high risk and low risk groups according to the age dependent thresholds. The best cut-points were determined considering the optimum sensitivity and specificity using receiver operating characteristic analysis.
Results: The age dependent intervention thresholds of major fracture risk ranged from 2.8 to 6.9% while hip fracture risk ranged from 0.4 to 3.0% between 50 and 80 years of age. Major fracture threshold of 3.75% and hip fracture threshold of 1.25% were the best fixed thresholds observed and non-inclusion BMD in the fracture risk estimations did not change the values. As a hybrid method, 3% major fracture and 1% hip fracture risks for those < 70 years old and age-dependent thresholds for those aged 70 years and above can be recommended.
Conclusions: The intervention thresholds estimated in the current study can be applied to identify Filipino postmenopausal women with a high fracture risk. Clinicians should decide on the type of thresholds most appropriate.

1. Introduction

Bone mineral density (BMD) measured by dual-energy X-ray absorptiometry (DXA) is widely used for the diagnosis of osteoporosis, an assessment fracture risk and monitoring osteoporosis specific treatment. Although BMD is a strong predictor of fracture, it alone has limited ability to target those with high fracture risk accurately. Johansson et al [1] found that intervention thresholds based on BMD alone are unable to identify women with higher fracture risk when compared with age-matched individuals without the addition of clinical risk factors, and this was particularly observed among older adults. Many studies have shown that clinical risk factors combined with BMD predict fractures more accurately than BMD alone, and this principle is used in fracture prediction models in many countries [2–4].

The Fracture Risk Assessment Tool (FRAX) introduced by the World Health Organization is widely used to target those with high fracture risk. A systematic review in 2016 found 120 patient management guidelines or academic papers recommending FRAX in osteoporosis patient care pathways [5]. It is recommended that fracture risk calculating algorithms and intervention thresholds should ideally be country and ethnicity specific to enhance their prediction accuracy [5,6]. The application of thresholds that have been developed for one country in another geographical setting is inappropriate due to the differences in fracture incidence, national mortality rates, prevalence of clinical risk factors, health care

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budget, practice guidelines, reimbursement policies, and health economic considerations. Furthermore, as the cost of interventions varies between countries, no one fixed FRAX threshold can be applied to all countries [4].

Country-specific FRAX models are currently available (FRAX v4.1) in 14 countries in Asia, 36 in Europe, 11 in Middle East and Africa, 2 in North America, 7 in Latin America, and 2 in Oceania (https://www.sheffield.ac.uk/FRAX/on June 21, 2021). Although FRAX has been made available in 72 countries and 81 different populations, the availability of country-specific or ethnic-specific intervention thresholds is limited. Kanis et al [5] in 2016 perusing 120 papers that recommended FRAX for patient management observed that 38 papers did not provide clear thresholds to identify those needing interventions. Most of the countries that have not made their own intervention thresholds have adopted the patient care pathway recommended by the National Osteoporosis Foundation (NOF) for the United States of America (USA) population [5]. The NOF recommended care pathway and intervention thresholds have been developed based on an economic analysis in 2008 and the application of these outside the USA is highly questionable [5].

The Philippines too has adopted the fracture probability cutoff values recommended by the NOF in the USA [7]. This consensus statement has been developed based on a systematic review of literature in 2011 and many Asian countries since then have developed their own intervention thresholds using scientific analyses [8–10]. Therefore, this study is designed to determine the thresholds that would help identifying Filipino postmenopausal women with high fracture risk in order to take appropriate therapeutic measures. We believe that country-specific intervention thresholds would enhance both the use of FRAX in patient evaluation and streamline the prescribing of anti-osteoporosis medications in the Philippines.

2. Methods

2.1. Study design

This was a single center cross sectional study on central DXA results of consecutive Filipino postmenopausal women aged 50 years or more, retrieved from a standalone bone densitometry unit in Metro Manila, Philippines from January 2014 to December 2019 by a trained technician. These patients had undergone DXA for clinical reasons to estimate either BMD or fracture risk. Patients with previous fragility fracture and those who had received any form of anti-osteoporosis medications were excluded. Further, those with technical faults in lumbar spine and/or hip scans or incomplete clinical data were also excluded. Age, weight, height, and the details of clinical risk factors that are included in FRAX fracture risk calculations were recorded using a pre-designed data collection sheet from all subjects. Data retrieved from DXA reports included areal BMDs (g/cm^2) at the femoral neck, total hip and lumbar spine (L1-L4).

Data on clinical risk factors were collected from the information provided by the referring clinician. This included past history of fragility fracture, parental history of hip fracture, use of glucocorticoids (> 3 consecutive months), co-morbidities and social habits such as alcohol use and smoking.

2.2. Methods for determining intervention thresholds

2.2.1. Age-dependent intervention thresholds

Age-dependent intervention thresholds were developed following on the rationale first developed by the National Osteoporosis Guideline Group (NOGG) in the United Kingdom (UK) and adopted subsequently by many other countries [8,9,11,12]. It states that if a woman with a prior fragility fracture is eligible for treatment, then a woman with the same fracture probability but without a fracture should also be eligible for such treatment. This rationale is applicable for all postmenopausal women regardless of age. Accordingly, intervention thresholds were calculated for a woman with body mass index (BMI) of 25 kg/m^2 aged 50–80 years with a previous fragility fracture without other clinical risk factors.

2.2.2. Fixed intervention thresholds

Fixed thresholds were developed using a database of 1546 postmenopausal women who underwent DXA between 2014 and 2019 and described above. Information on clinical risk factors had been collected using a pre-designed questionnaire at the time of DXA scanning and all women had undergone BMD measurements adhering to the manufacturer's protocols (Hologic Inc; Bedford, MA, USA). The in-vitro precision of the machine (spine coefficient of variation < 1.0%) had been verified on every scanning day by calibrating the phantoms provided by the manufacturer.

Major osteoporosis fracture and hip fracture risks were estimated based on the Philippines FRAX algorithm using clinical risk factors with and without femoral neck BMD input separately. Women were categorized to 2 risk groups: high risk group requiring intervention (equal or above the age dependent ITs) and low risk group not requiring intervention (below the age dependent ITs). Receiver operating characteristic (ROC) analyses were performed with the risk category as the dependent variable (dichotomous manner), and major and hip fracture risks as independent variables. The best cut-points (fixed thresholds) for both major fracture and hip fracture risks were determined selecting the point closest to the top left corner of the area under curve (AUC). These cutpoints were confirmed by the Youden index [sensitivity + (1-specificity)] [13] and in a given Youden index, the point that gave the best sensitivity and specificity (partial Youden index) [14].

2.2.3. Hybrid intervention thresholds

Hybrid ITs were developed adhering to the method previously followed by Chakhtoura et al [15] and Lekamwasam et al [8]. In this analysis, age dependent ITs were described for women aged $\geq$ 70years and fixed ITs were developed for women aged < 70years.

This study was approved by the University of Santo Tomas Hospital Research Ethics Board (REC-2020-06-078-MD). Informed consent of subjects was waived by the NWDi and their Data Privacy Officer.

3. Results

The main characteristics of 1546 women included in the analysis are given in Table 1. Diabetes and breast cancer were the most prevalent diseases while 16% were on thyroid hormone replacement therapy.

3.1. Age dependent intervention thresholds

The age-dependent intervention thresholds of major osteoporotic fracture risk ranged from 2.8% to 6.9% and hip fracture risk ranged from 0.4% to 3.0% between 50 and 80 years (Table 2; Figs. 1 and 2).

3.2. Fixed intervention thresholds

Major osteoporosis fracture threshold of 3.75% and hip fracture risk threshold of 1.25% were the best cutoff values observed and inclusion BMD in the fracture risk estimations did not change them. Thresholds estimated without BMD, however, showed higher sensitivity compared to those calculated with BMD input (Table 3).

Table 1
Characteristics of 1546 postmenopausal women included in the analysis.

Variable	Mean (SD)
Age (yr)	66.2 (9.9)
BMI (kg/m^2)	24.9 (4.3)
Femoral neck BMD (g/cm^2)	0.622 (0.120)
	Number (%) or %
Early menopause (< 45 years)	236 (15.23%)
Premature menopause (< 40 years)	75 (4.8%)
Average MOF risk (with BMD)	3.2%
Average MOF risk (without BMD)	3%
Average HF risk (with BMD)	1%
Average HF risk (without BMD)	1%
Smokers (past and current)	61 (3.9%)
Alcohol consumers	7 (0.4%)
Glucocorticoid use of > 3 months at one time	11 (0.7%)
Systemic lupus erythematosus	3 (0.19%)
Rheumatoid arthritis	13 (0.8%)
Diabetes mellitus type 2	461 (29.8%)
On thyroid medication	248 (16%)
Breast cancer undergone radical mastectomy	150 (9.7%)
Breast cancer, on aromatase inhibitor	48 (3.1%)
Renal transplant	22 (1.4%)
Family history of osteoporosis	2 (0.13%)
Chronic kidney disease	10 (0.65%)

SD, standard deviation; BMI, body mass index; BMD, bone mineral density; MOF, major osteoporotic fracture; HF, hip fracture.

Table 2
Age dependent major osteoporosis fracture and hip fracture intervention thresholds estimated based on the Philippines FRAX model.

Age	Major fracture thresholds (%)	Hip fracture thresholds (%)
50 years	2.8	0.4
55 years	3.6	0.7
60 years	4.7	1.0
65 years	5.5	1.3
70 years	6.3	1.8
75 years	6.9	2.4
80 years	6.4	3.0

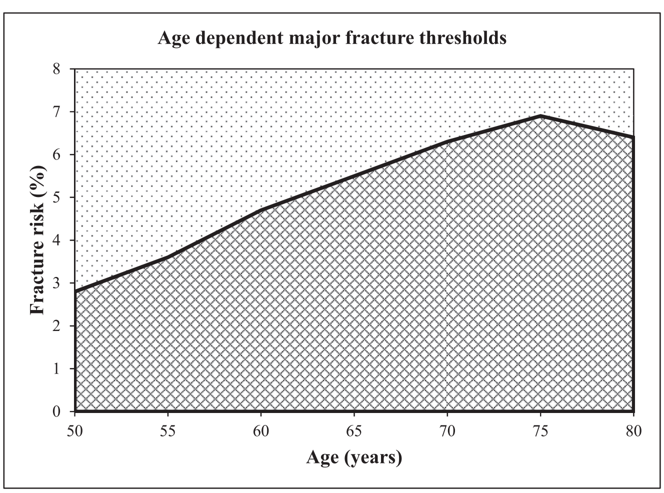

Fig. 1. Age-dependent intervention thresholds of major fracture risk.

3.3. Hybrid intervention thresholds

When those 70 years old and below were reanalyzed, the most appropriate fixed intervention thresholds found were; major fracture risk 3.0% and hip fracture risk 1.0%. The inclusion of BMD in the risk assessment did not change the values. To develop hybrid thresholds, these values were combined with age dependent ITs were calculated previously (Table 1) for those over 70 years of age.

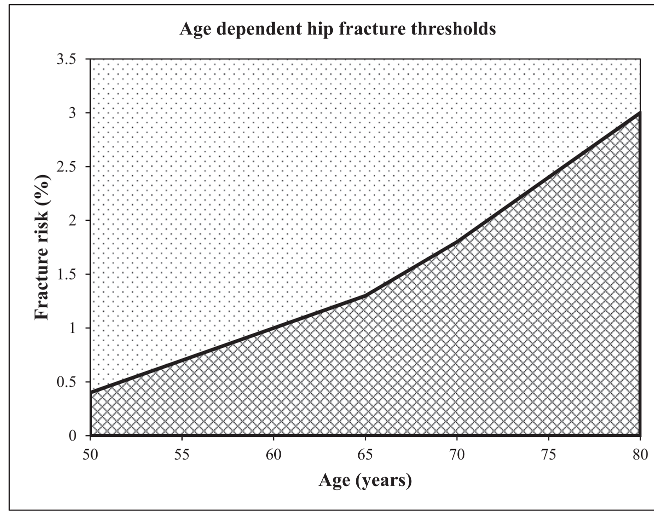

Fig. 2. Age-dependent intervention thresholds of hip fracture risk.

Table 3
Performance of fixed major osteoporosis and hip fracture thresholds with and without BMD input.

Criterion	AUC (SE)	IT%	Sensitivity	Specificity
Major fracture without BMD input	0.94 (0.01)	3.75	0.93	0.81
Hip fracture without BMD input	0.94 (0.01)	1.25	0.94	0.78
Major fracture with BMD input	0.86 (0.01)	3.75	0.74	0.84
Hip fracture with BMD input	0.89 (0.01)	1.25	0.80	0.81

AUC, area under receiver operating characteristic (ROC) curve; SE, standard error; IT, intervention threshold; BMD, bone mineral density.

4. Discussion

In the current study we attempted to develop country-specific intervention thresholds for FRAX based fracture probabilities in the management of postmenopausal osteoporosis in the Philippines. The method used in this analysis is widely known and described in many previous studies of similar nature [8,9]. Due to the lack of scientifically validated thresholds, clinicians in the Philippines are compelled to use guidelines developed elsewhere. The suitability of such guidelines developed in a different country is questionable.

The age dependent major fracture thresholds in the current study ranged from 2.8% to 6.9% between 50 and 90 years while the corresponding values of hip fracture ranged from 0.4% to 3%. These figures are somewhat lower when compared with the age dependent thresholds reported from Asian countries such as China [16], India [10], Japan [17], Singapore [9] and Sri Lanka [8]. The fixed thresholds observed for major fracture and hip fracture risks in the current study were 3.75% and 1.25%, respectively. Similar figures have been observed by Zhang et al [18] in China in 2014 (4.0% and 1.3%) and Chandran et al [9] for Singaporean Malay and Indian populations. In the latter, the fixed thresholds of major osteoporosis fracture and hip fracture for Malay and Indian populations were 2.5/0.25% and 2.5/1.0%, respectively.

The wide variation of intervention thresholds recommended or practiced in different countries in the Asian region is well known [19]. This could partly be due to the inherent differences in the country specific FRAX algorithms in this region. FRAX algorithms are built using country specific fragility fracture rates and national mortality data; hence a geographical variation in fracture risk estimations is expected. The major fracture risk of a 65 year old woman of 25 BMI (kg/m^2) without clinical risk factors varies from 2.8% in the Philippines, the lowest estimate in the Asian region, to 7.7% in Taiwan. Furthermore, fracture risk estimations for the given clinical scenario are higher for Chinese both in China (3.8%) and Singapore (6.3%), Singaporean Malay and Indian (6.7% and 6.3%, respectively), and South Koreans (6.0%).

Apart from the inherent differences in FRAX models, the diversity of methodologies used to generate intervention thresholds is a potential source of the observed variation [19]. The thresholds recommended by the NOF in the USA are based on an economic evaluation while the NOGG in the UK uses a more clinically oriented approach, and in a given clinical setting the proportion of individuals qualifying for treatment and subsequently treatment related expenditures depend on the algorithm used to analyze them [20,21]. In the Asian region, China [16] and Taiwan [22] have defined thresholds based on economic evaluations, while Japan [23] has determined the thresholds in such a way that demarcates the proportion of women with fracture risk in the population. Although India [10], Sri Lanka [8], and Singapore [9] have followed the same method that was used in the current study, the thresholds estimated in these analyses are not concordant.

We used the rationale originally proposed by the NOGG in the UK [11] and followed by many researches afterwards [5]. It is based on the premise that if a postmenopausal woman with an incident fragility fracture qualifies for specific therapy regardless of age and BMD, then a same age woman with no fracture but has same fracture risk also qualifies for such treatment. While this argument was used to generate age dependent intervention thresholds, the fixed thresholds were developed by selecting a cut point that gave the highest combined sensitivity and specificity. The hybrid thresholds were developed to overcome the possibility that age dependent thresholds may lead to overtreatment of young people [15]. In hybrid thresholds, the limitations related to the use of age dependent threshold in old age still prevails.

The type of thresholds most appropriate to a country needs to be decided locally taking factors such as health economics, availability of health resources, and clinicians' preferences into consideration. Fixed values are user-friendly; hence they are widely used. In contrast, age dependent thresholds are not easily recallable therefore should be made easily accessible to clinicians at the point-of-care. While fixed thresholds can potentially lead to under-treatment of young and overtreatment of old adults, age dependent thresholds lead to under-treatment of older adults. When adapting fixed thresholds, it is mandatory to treat all postmenopausal women with incident fragility fracture to overcome the underestimation of fracture risk of young people with prior fracture and missing out treatment.

The non-inclusion of BMD did not change the cut points in both major and hip fracture risks estimated by the Philippines FRAX model. This will allow clinicians with restricted access to DXA facility to initiate treatment purely based on clinical risk factors. Although some countries recommend different thresholds for treatment and referral to DXA, the current analysis indicates that clinicians need not delay the decision to initiate medications while waiting for DXA evaluation, if that is deemed necessary for other reasons.

Studies have shown that clinicians prefer to have their own country specific FRAX estimations when treatment decisions are made [24]. Country specific FRAX algorithms supplemented with appropriate intervention thresholds are helpful to enhance uniform and rational treatment decision making across the country. Further, the wide application of these thresholds in patient management would help identifying their limitations and weaknesses.

A study of cohort design is the most appropriate method to determine accurate intervention thresholds. However this is expensive and requires long period of follow-up. Although not most appropriate, many countries have followed the method used in this analysis. The prevalence of clinical risk factors is likely to vary based on the clinical situation and patient characteristics and it is important to replicate this analysis in different locations to check whether results are reproducible. The majority of patients (about 80%) included in this study were from the National Capital Region (NCR) and from urban settings. The rest were patients referred from nearby provinces of Luzon (15%) and Visayas and Mindanao (5%). However the ethnic distribution of the study sample was comparable to the country's ethnic composition.

The determination of intervention thresholds requires a representative sample of patients to whom the thresholds are subsequently applied. Accordingly, we used a sample of postmenopausal women who underwent DXA for clinical reasons and the results of the current study can only be applied to postmenopausal women in the Philippines. These women have been referred by clinicians for the evaluation of fracture risk due to the presence of clinical risk factors of either osteoporosis or fracture.

5. Conclusions

This study recommends 3 different types of intervention thresholds to identify those with high fracture risk when using the Philippines FRAX model. They have inherent weaknesses and advantages and clinicians should decide the best option that suits the local conditions. These thresholds are more suitable for making therapeutic decisions in order to offer anti-osteoporosis medication for postmenopausal women with high risk of fragility fracture.

CRediT author statement

Julie Li-Yu: Conceptualization, Resources, Writing – original draft, Writing – review & editing. **Sarath Lekamwasam:** Formal analysis, Writing – original draft.

Conflicts of interest

The authors declare no competing interests.

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References

[1] Johansson H, Azizieh F, Al Ali N, Alessa T, Harvey NC, McCloskey E, et al. FRAX- vs. T-score-based intervention thresholds for osteoporosis. Osteoporos Int 2017;28:3099–105.
[2] Johansson H, Kanis JA, Oden A, Johnell O, McCloskey E. BMD, clinical risk factors and their combination for hip fracture prevention. Osteoporos Int 2009;20:1675–82.
[3] Johansson H, Kanis JA, McCloskey EV, Odén A, Devogelaer JP, Kaufman JM, et al. A FRAX® model for the assessment of fracture probability in Belgium. Osteoporos Int 2011;22:453–61.
[4] El-Hajj Fuleihan G, Chakhtoura M, Cauley JA, Chamoun N. Worldwide fracture prediction. J Clin Densitom 2017;20:397–424.
[5] Kanis JA, Harvey NC, Cooper C, Johansson H, Odén A, McCloskey EV. A systematic review of intervention thresholds based on FRAX. Arch

Osteoporos 2016;11:25.
[6] Leslie WD, Brennan SL, Lix LM, Johansson H, Oden A, McCloskey E, et al. Direct comparison of eight national FRAX® tools for fracture prediction and treatment qualification in Canadian women. Arch Osteoporos 2013;8:145.
[7] Li-Yu J, Perez EC, Cañete A, Bonifacio L, Llamado LQ, Martinez R, et al. Consensus statements on osteoporosis diagnosis, prevention, and management in the Philippines. Int J Rheum Dis 2011;14:223–38.
[8] Lekamwasam S, Chandran M, Subasinghe S. Revised FRAX®-based intervention thresholds for the management of osteoporosis among postmenopausal women in Sri Lanka. Arch Osteoporos 2019;14:33.
[9] Chandran M, McCloskey EV, Thu WPP, Logan S, Hao Y, Tay D, et al. FRAX® based intervention thresholds for management of osteoporosis in Singaporean women. Arch Osteoporos 2018;13:130.
[10] Nagendra L. FRAX-based osteoporosis treatment guidelines for resource-poor settings in India. Arch Osteoporos 2021;16:69.
[11] Compston J, Bowring C, Cooper A, Cooper C, Davies C, Francis R, et al. Diagnosis and management of osteoporosis in postmenopausal women and older men in the UK: national Osteoporosis Guideline Group (NOGG) update 2013. Maturitas 2013;75:392–6.
[12] Compston J, Cooper A, Cooper C, Gittoes N, Gregson C, Harvey N, et al. UK clinical guideline for the prevention and treatment of osteoporosis. Arch Osteoporos 2017;12:43.
[13] Youden WJ. Index for rating diagnostic tests. Cancer 1950;3:32–5.
[14] Li C, Chen J, Qin G. Partial Youden index and its inferences. J Biopharm Stat 2019;29:385–99.
[15] Chakhtoura M, Leslie WD, McClung M, Cheung AM, Fuleihan GE. The FRAX-based Lebanese osteoporosis treatment guidelines: rationale for a hybrid model. Osteoporos Int 2017;28:127–37.
[16] Cui L, He T, Jiang Y, Li M, Wang O, Jiajue R, et al. Predicting the intervention threshold for initiating osteoporosis treatment among postmenopausal women in China: a cost-effectiveness analysis based on real-world data. Osteoporos Int 2020;31:307–16.
[17] Fujiwara S, Nakamura T, Orimo H, Hosoi T, Gorai I, Oden A, et al. Development and application of a Japanese model of the WHO fracture risk assessment tool (FRAX). Osteoporos Int 2008;19:429–35.
[18] Zhang Z, Ou Y, Sheng Z, Liao E. How to decide intervention thresholds based on FRAX in central south Chinese postmenopausal women. Endocrine 2014;45:195–7.
[19] Lekamwasam S. The diversity of fracture risk assessment tool (FRAX)-based intervention thresholds in Asia. Osteoporos Sarcopenia 2019;5:104–8.
[20] Kyriakos G, Vidal-Casariego A, Fernández-Martínez MN, Blanco-Suárez MD, Ballesteros-Pomar MD, Cano-Rodríguez I. Impact of the NOGG and NOF Guidelines on the indication of bone mineral density in routine clinical practice. J Clin Densitom 2015;18:533–8.
[21] Kyriakos G, Vidal-Casariesgo A, Quiles-Sánchez LV, Urosa-Maggi JA, Calleja-Fernández A, Hernández-Moreno A, et al. Osteoporosis management in a real clinical setting: heterogeneity in intervention approach and discrepancy in treatment rates when compared with the NOGG and NOF Guidelines. Exp Clin Endocrinol Diabetes 2016;124:466–73.
[22] Chan DC, McCloskey EV, Chang CB, Lin KP, Lim LC, Tsai KS, et al. Establishing and evaluating FRAX(®) probability thresholds in Taiwan. J Formos Med Assoc 2017;116:161–8.
[23] Kanis JA, Johansson H, Odén A, McCloskey EV. The distribution of FRAX(®)-based probabilities in women from Japan. J Bone Miner Metabol 2012;30:700–5.
[24] Korthoewer D, Chandran M. Osteoporosis management and the utilization of FRAX®: a survey amongst health care professionals of the Asia-Pacific. Arch Osteoporos 2012;7:193–200.