

EDITORIAL UVODNIK

INTERVENTION THRESHOLDS IN CHRONIC NCDs WITH A FOCUS ON CARDIOVASCULAR DISEASE AND OSTEOPOROSIS

PRAGOVI INTERVENCIJE KOD HRONIČNIH NNCD SA FOKUSOM NA KARDIOVASKULARNE BOLESTI I OSTEOPOROZU

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Introduction

It is well established that the majority of the global burden of health-related morbidity and mortality arises from chronic Non-Communicable Diseases (NCDs) such as cardiovascular disease (CVD), cancer, diabetes and respiratory diseases [1]. This identification of 4 'main' NCDs by the World Health Organisation (WHO) has led to many countries prioritising these conditions, but musculoskeletal conditions, such as osteoarthritis and osteoporosis, have often received less policy attention despite their substantial burden of disability. For example, in an analysis of the global burden of disease in the United Kingdom (UK), the greatest contribution to years lived with disability was highest (30%) for those living with musculoskeletal disorders, with mental and behavioural disorders as the second most common cause [2]. However, in 2023, as part of the UN Decade of Healthy Ageing, WHO launched a new Bone Health and Ageing initiative, the primary goals of which are to develop a strategic roadmap for optimizing bone health to promote healthy ageing and to advocate for a public health strategy to prevent fractures among older people [3].

NCDs are usually multifactorial in causation, including lifestyle factors (e.g. obesity, smoking, alcohol intake, lack of exercise) and clinical or biological risk factors; the latter range across different types of factors ranging from dichotomous (Yes/No) risk factors (e.g. a family history of the disease, the presence of other associated diseases) or other contributory clinical/biological risk factors that frequently have a continuous relationship between the factor and the risk of disease outcomes (e.g. higher blood pressure and

stroke, higher cholesterol and myocardial infarction, lower bone mineral density and fracture). These continuous clinical risk factors are often classified as diseases, such as hypertension, hypercholesterolaemia and osteoporosis, using thresholds which allow examination of the prevalence of the diseases globally and regionally. Frequently, these same thresholds are used as intervention thresholds (e.g. blood pressure above 140/90mm Hg, bone mineral density (BMD) T-score ≤ -2.5) and, in many healthcare systems, the diagnosis provides access to reimbursement of treatment costs. Until now in many healthcare settings, these thresholds have often played a central role in how clinicians decide when to start, intensify or stop treatments in patients with chronic NCDs, but the main limitation is that intervention based on a single risk factor ignores the input from other risk factors. This article addresses concepts of outcome risk, approaches to defining and applying intervention thresholds, and illustrates these issues in the setting of CVD and osteoporosis.

Outcome risk in NCDs and its role in disease management

Traditionally, as noted above, pharmacological management has been based around thresholds within individual risk factors which have been characterised as independent diseases. However, the fact that this approach is focussed on intervention thresholds based on a single risk factor in a multifactorial disease is increasingly coming under scrutiny. It is increasingly recognised that the management of NCDs should be organised around quantified estimates of

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Abbreviations

NCDs	– Non-Communicable Diseases
CVD	– cardiovascular disease
WHO	– World Health Organisation
BMD	– bone mineral density
BMI	– body mass index
SBP	– systolic blood pressure
DBP	– diastolic blood pressure
MRC	– Medical Research Council
SCOOP	– Screening of Older women for Prevention
FRAX	– Fracture Risk Assessment Tool
SBP	– systolic blood pressure
ESC	– European Society of Cardiology
NICE	– National Institute for Health and Care Excellence
UK	– United Kingdom
NOGG	– National Osteoporosis Guideline Group
LAT	– lower assessment thresholds
IT	– intervention thresholds
UAT	– upper assessment thresholds

an individual's future outcome risk rather than single risk factors in isolation. In the setting of osteoporosis and the role of BMD, this distinction between its use for diagnostic and intervention thresholds was already acknowledged in the original WHO report that established the T-score threshold for osteoporosis in 1994. "As a diagnostic tool, it (BMD) gives information concerning the presence or absence of the disease with the cut-off values chosen. Its potential as a prognostic tool is to determine the future probability of osteoporosis or, better, the probability of fragility fractures where different cut-off values may be used. In this sense, bone density values are used as a risk factor. Useful analogies may be drawn with other diseases for which major risk factors have been identified" [4].

The outcome risk is usually expressed as the risk or probability that a clinically relevant event (for example myocardial infarction, stroke, osteoporotic fracture or death) will occur over a specified time horizon, most often the next 10 years. In CVD, examples of risk prediction models estimate the likelihood of events such as non-fatal myocardial infarction, stroke, or cardiovascular death using combinations of age, sex, blood pressure, lipids, smoking and diabetes, and sometimes additional biomarkers (**Figure 1**) [5–7]. In contrast to being above or below the 'diagnostic' thresholds, these models use the actual values of the continuous varia-

bles (e.g. blood pressure, cholesterol) as the input to the calculations. Similarly, in osteoporosis, fracture risk calculators such as Fracture Risk Assessment Tool (FRAX) (**Figure 1**) [8–10], QFracture [11,12] and the Garvan fracture risk calculator, [13] combine a number of clinical risk factors (e.g. age, body mass index (BMI), prior fracture, parental hip fracture, smoking, alcohol intake, glucocorticoid use, and causes of secondary causes, etc.). Unlike the FRAX and Garvan tools, QFracture does not accommodate the optional use of BMD; within the FRAX and Garvan tools, BMD is used as a continuous variable (e.g. the actual BMD or T-score) rather than simply being above or below the thresholds for BMD-defined osteoporosis.

The rationale for using outcome risk as the driver for intervention in chronic NCDs arises from several considerations. Firstly, treatment benefit is usually proportional to baseline risk: individuals at higher baseline risk gain greater absolute risk reductions for the same relative treatment effect. For example, the use of alendronate in osteoporosis is associated with a relatively consistent relative risk reduction across the spectrum of fracture risk, but with a greater absolute benefit amongst women with highest FRAX scores [14]. **In addition, some osteoporosis therapies show evidence of an increased relative efficacy in patients at higher risk [15,16]. Secondly, interventions have costs, inconvenience and potential harms, which makes it desirable to target those most likely to benefit sufficiently to justify the intervention.** Finally, the majority of health systems operate under limited resources so that prioritising high-risk groups can improve cost-effectiveness and population impact. For example, in the Medical Research Council (MRC)-funded population-based Screening of Older women for Prevention (SCOOP) study in the UK, FRAX was used to target treatment to women age 70–85 years at high risk of hip fracture. In this study, treatment was given to only 14% of women in the intervention group but led to an overall 28% reduction in hip fractures compared to standard care, an approach that was highly cost-effective/cost-saving [17–20].

Diagnostic and intervention thresholds: confusion if accepted to be identical

It is important to distinguish between diagnostic and intervention thresholds. An individual can be formally labelled as having a disease (diagnosis), but this does not automatically mean that medications or other treatments are legally or clinically required (intervention). The diagnosis usually means that management, but not necessarily treatment, is required. For diseases arising from risk factors that have a continuous relationship to a clinical outcome, diagnostic

European HeartScore	ASCVD (US) model	FRAX model
• Age • Sex • Currently Smoker? • Systolic BP (mm Hg) • Total Cholesterol (mg/dL) • HDL Cholesterol (mg/dL)	• Age • Sex • Currently Smoker? • Systolic BP (mm Hg) • On Hypertension Treatment? • Diabetes? • Total Cholesterol (mg/dL) • HDL Cholesterol (mg/dL) • Race/ethnicity	• Age • Sex • Currently Smoker? • Prior fracture? • Parental hip fracture? • Glucocorticoid use? • Rheumatoid arthritis? • Secondary osteoporosis? • Alcohol excess? • BMD (femoral neck – optional)

Figure 1. Variables included in examples of CVD risk assessment tools and the FRAX tool for osteoporosis

thresholds provide an operational definition of the disease, such as hypertension or osteoporosis, to aid classification and epidemiological surveillance of the disease, but do not necessarily specify when treatment should start. The conflation of diagnostic thresholds and intervention thresholds, frequently complicated by healthcare payers deciding to only reimburse medication costs when the diagnosis is present, can cause confusion in clinical practice in a number of ways. Firstly, the belief that diagnosis and intervention are inextricably linked implies that if the intervention threshold needs to be altered, then the disease needs to be redefined with new diagnostic thresholds. An example was provided in the 2017 ACC/AHA Guideline for High Blood Pressure in which the guidance moved away from the long-established diagnostic threshold of systolic blood pressure (SBP)/diastolic blood pressure (DBP) of $\geq 140/90$ mmHg and redefined hypertension as stage 1 hypertension (SBP 130-139/DBP 80-89 mmHg) and stage 2 hypertension (SBP/DBP $\geq 140/90$ mmHg) [21]. Despite zero change in the absolute risk of stroke, this suggested change in thresholds had a potentially dramatic impact on the global prevalence of hypertension. For example, in a study of over 4 million adults participating in the global May Measurement Month initiative, the new thresholds increased the prevalence of hypertension by 72% among the participating countries, an impact that was most pronounced in low-income countries and raised questions about the need for further epidemiological studies in dedicated population studies [22].

A similar approach to 'better' target interventions in osteoporosis has been suggested, but the latter promotes the setting of different country-specific or population-specific T-score thresholds so that osteoporosis BMD-based definitions would be numerous and confusing [23]. The desire to alter or adapt the T-score was so that the T-score threshold would be set at the value that represented the same absolute risk of fracture across populations. However, the objective of the T-score definition was to allow comparison of the prevalence of BMD below a certain threshold, rather than define a threshold of fracture risk. Of course, BMD is an important risk factor for fracture but the incidence of the latter is influenced by many other factors, some of which are known and others not yet well-defined, with variability between and across populations. The variability in fracture risk between different populations and ethnicities is much greater than the variability in BMD [24,25]. This is recognised by the need for numerous FRAX models which calibrate the risk assessment to the actual age and sex-specific incidence of fracture and mortality within different populations and ethnicities.

Limitations of single risk factor thresholds in multifactorial diseases

An important conceptual distinction is the difference between the risk arising from a single risk factor defined disease (e.g. hypertension as defined by set systolic and diastolic blood pressures or osteoporosis as defined by BMD T-scores) and the risk of the actual clinical outcomes attributable to a combination of that disease and other risk factors. Until recently, intervention thresholds have been established and used for reimbursement in these single risk factor diseases (e.g. hypertension, hyperlipidaemia, osteoporosis), a decision that impacts on the actual risk profile of the population treated in terms of their risk of the disease outcome as it disregards the presence or absence of other risk factors. Increasingly, contemporary guidelines are recommending that treatment thresholds should embrace the actual outcome risk, expressed in terms of predicted absolute CVD or fracture risk, rather than isolated blood pressure or BMD cut-offs. An example of the data analysis that supports this approach was a published meta-analysis of treatments for hypertension using individual-level data from 48 randomised trials of pharmacological blood pressure lowering medications versus placebo or other classes of blood pressure-lowering medications [26]. **Data were pooled to investigate the effects of blood pressure-lowering treatment in participants, with and without prevalent cardiovascular disease, overall and across seven systolic blood pressure categories (ranging from <120 to ≥ 170 mm Hg).** In a total of 344 716 participants from 48 randomised clinical trials, 31 239 (9.8%) of participants with previous cardiovascular disease and 14 928 (8.0%) of individuals without previous cardiovascular disease had a baseline SBP of less than 130 mm Hg. In participants with and without previous cardiovascular disease, the incidence rate for developing a major cardiovascular event was lower in the intervention groups than in the comparator group with similar reductions of cardiovascular events per 5 mm Hg reduction in SBP across the two groups. Importantly, in the SBP stratified analyses, there was no reliable evidence of heterogeneity of treatment effects on major cardiovascular events by baseline cardiovascular disease status or systolic blood pressure categories (data from those without baseline cardiovascular events shown in **Figure 2**). The authors concluded that a fixed degree of pharmacological blood pressure lowering is similarly effective for primary and secondary prevention of major cardiovascular disease, even at blood pressure levels currently not considered for treatment. They concluded that the findings should dismiss "the suggestions that blood pressure-lowering treatment is only effective when

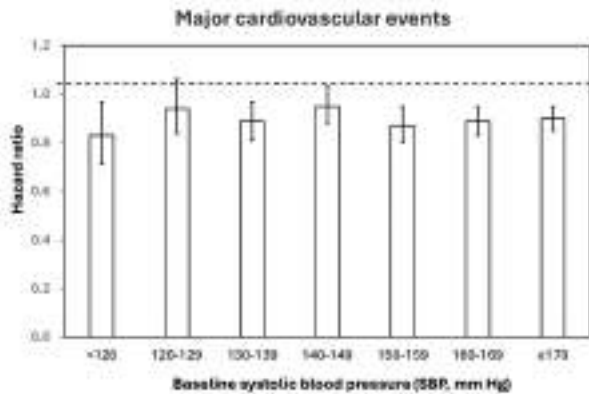


Figure 2. Effect of anti-hypertensive treatment on the risk of cardiovascular events across categories of baseline SBP in patients without previous CVD at baseline. There was no significant interaction of efficacy with baseline SBP (unadjusted interaction p-value 0.66, adjusted 1.0) with similar reductions in events at low and high baseline SBP. Adapted from [26].

blood pressure is above a certain threshold”, an erroneous belief that has been mirrored in the claims that treatments of osteoporosis are ineffective in patients with BMD values above the T-score threshold of -2.5 [27]. In osteoporosis there is now overwhelming evidence that treatments are similarly effective in many patients and clinical scenarios where the BMD is not osteoporotic [27]. This is in keeping with the recognition in the WHO 1994 report that different thresholds could be used to target interventions when BMD is used as a predictor of fracture risk rather than simply defining the presence of BMD-defined osteoporosis [4]. A further paper from key authors in the hypertension study reported above, subsequently published a paper calling for an increasing role of CVD risk prediction in clinical practice for BP treatment allocation and a cultural shift in how blood pressure is treated; “It is time for us to recognize that the objective is to treat cardiovascular disease risk not just hypertension” [28].

Intervention thresholds using outcome risks

In contrast to a diagnostic threshold, an intervention threshold can generally be characterised as the level of predicted outcome risk at which the expected benefits of a preventive or therapeutic intervention are judged to outweigh the harms and costs. As outcome risk is typically modelled as a continuous variable, clinical decision-making therefore requires choosing cut-offs or “thresholds” that translate a continuum of risk into discrete categories such as low, intermediate, high or very high risk. Different methods of deciding such thresholds are used in practice, including purely

clinical thresholds (based on expert consensus about benefit–harm trade-offs), cost-effectiveness thresholds (incorporating formal economic modelling), and pragmatic or policy thresholds that reflect local resources and priorities.

Intervention thresholds may be expressed as fixed or age-dependent risk thresholds. In the management of CVD, most international guidelines endorse fixed risk thresholds across the age range [29]. However, the 2021 European Society of Cardiology (ESC) CVD prevention guidelines introduced new age-specific risk thresholds for primary prevention, to address the concern that uniform age-independent cut-offs could result in over-treatment of older adults and under-treatment of younger adults [30]. This approach was subsequently reversed in the 2024 ESC guidelines for the management of elevated BP and hypertension which returned to a single age-independent CVD risk threshold because of concerns that the age-dependent approach could withhold CVD preventive treatment for older adults based solely on age [29,31].

A systematic review of FRAX-based thresholds identified that most guidelines used fixed or age-independent thresholds for major osteoporotic fracture and hip fracture [32]. Many guidelines use thresholds derived from a US threshold cost-effectiveness analysis which generated thresholds of 20% for MOF and 3% for hip [33], despite the fact that this cost-effectiveness analysis is now out-of-date and the thresholds may not be appropriate for lower risk countries or ethnicities. The impact of basing intervention thresholds on cost-effectiveness analysis can lead to controversial outcomes as illustrated by a NICE analysis of bisphosphonate treatments in osteoporosis in the United Kingdom (UK) in 2017. [34]. This recommended that, amongst individuals who qualify for osteoporosis assessment on the basis of the previously published National Institute for Health and Care Excellence (NICE) Fracture Risk Assessment Clinical Guideline (CG146, [35] treatment with oral bisphosphonates could be instituted at a 10-year probability of major osteoporotic fracture above 1%, or above 10% for intravenous bisphosphonates, thresholds which could have caused confusion as potential intervention thresholds [36].

As noted above in the CVD field, age-independent thresholds can impact on the equity of access to treatment across age ranges. In practice, they generally decrease access at younger ages and may lead to overtreatment at older ages [37]. To counter this, age-dependent intervention thresholds are utilised in many guidelines, initially led by the National Osteoporosis Guideline Group (NOGG) in the UK. These thresholds are clinical thresholds based on the consensus that if a woman with a prior fracture can be considered for intervention,

then a patient of the same age without a fracture but the same level of fracture risk should also be considered for treatment. This permits identification of those at highest risk at all ages so that treatment can be introduced not only to decrease that risk in the short-term but to also limit the increase in risk over time [38].

The UK National Osteoporosis Guideline Group has operationalised this approach by defining age-specific lower assessment thresholds (LAT), intervention thresholds (IT) and upper assessment thresholds (UAT) based on FRAX-estimated 10-year fracture probabilities [39–41]. In the latest NOGG guidelines, a “very high risk” category, using a FRAX-based fracture probability exceeding the intervention threshold by 60%, has also been defined to identify patients who should be referred to specialist services for more intensive assessment and treatment planning, particularly with attention to bone-forming agents as first line therapy.

Summary and Conclusion

The decoupling of diagnostic and intervention thresholds has several important clinical implications. First, it legitimises offering treatment to individuals who do not meet the bone mineral density definition of osteoporosis but have fracture probability above the intervention threshold, such as younger adults without prior fragility fracture and “osteopenic” bone mineral density but with one or more other clinical risk factors. Second, it avoids automatic treatment of all individuals with bone mineral den-

sity T-score ≤ -2.5 , particularly older patients whose absolute fracture risk may be modest compared to the wider age-matched population. Nonetheless, the co-existence of diagnostic and intervention thresholds can create confusion among clinicians and patients. Some may incorrectly equate a diagnosis of osteoporosis with an obligation to treat pharmacologically, while others may falsely reassure high-risk individuals with “normal” or “osteopenic” bone mineral density, overlooking elevated fracture risk due to age and other clinical risk factors. Under-treatment remains a significant problem, with large proportions of high-risk individuals not receiving osteoporosis medications despite clear guideline indications.

However, it is increasingly clear that outcome risk and intervention thresholds offer a coherent framework for prioritising prevention and treatment in chronic non-communicable diseases, including cardiovascular disease and osteoporosis. Despite methodological and implementation challenges, risk-based thresholds enable more rational, transparent and cost-effective use of limited healthcare resources, provided they are regularly updated (without having to redefine the disease), locally calibrated and applied with sound clinical judgement. As populations age and the burden of chronic NCDs continues to rise, coherent and well-implemented strategies for defining and applying outcome-based intervention thresholds will be essential for maximising health gains and minimising the harms and costs of both under- and over-treatment.

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