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Impact of Italian Medicines Agency Note 96 on the use of vitamin D in Italy

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Vitamin D plays a key role in maintaining serum calcium levels required for musculoskeletal health and bone metabolism within their natural physiological range.[1]

Vitamin D ensures proper bone mineralisation. Vitamin D deficiency is a risk factor for skeletal fragility in the elderly and osteoporotic fractures.[2,3] Moreover, scientific studies have shown that Vitamin D supplementation prevents systemic bone loss following a fracture and reduces the risk of multiple fractures.[4,5]

National and international guidelines on the management of osteoporosis recommend adequate calcium and vitamin D supplementation in addition to anti-osteoporotic therapies.[6,7]

AIFA Note 79, in defining which drugs for primary and secondary prevention of the risk of osteoporotic fractures are reimbursable, states that, before starting therapy with these drugs, an adequate intake of calcium and vitamin D is recommended, resorting, where diet and sun exposure are inadequate, to supplements with calcium salts and vitamin D3 (and not its hydroxylated metabolites).[8]

In recent years, a progressive increase in the consumption of vitamin D in Italy, has brought about a consequent increase in expenditure by the National Health Service (NHS).[9,10] The growth in the consumption of Vitamin D led to speculation of possible inappropriate use. Consequently, in late October 2019, AIFA published Note 96 identifying the criteria for the reimbursement of Vitamin D supplementation for the prevention and treatment of vitamin deficiency in adults.[11]

In the first 15 months of application of the Note, there was nearly a 30% decrease in the consumption of and expenditure for Vitamin D compared to previous periods.[12] However, whether this is due to an improvement in the appropriateness of use is not clear.

Recently, CliCon S.r.l. Benefit Corporation, in cooperation with Azienda ULSS Berica 8 Local Health Service, conducted an analysis to verify whether the reduction in vitamin D consumption observed after Note 96 became effective was accompanied by an increase in the appropriateness of the use of these supplements. The results were presented at the last edition of the ISPOR 2021 European Conference.[13] The analysis was performed using the Local Health Service's administrative flows. All adult patients with at least one prescription for the pharmaceutical products in Note 96 (cholecalciferol, cholecalciferol/calcium salts, calcifediol) or in Note 79 (bisphosphonates, teriparatide, strontium ranelate, raloxifene, denosumab, bazedoxifene) in the 12 months before (1/10/2018 to 30/09/2019) and after (1/10/2019 to 30/09/2020) when Note 96 entered into force, were included. Improvement in the appropriateness of prescriptions, measured as a reduction in the deviation between clinical practice and therapeutic recommendations, was assessed using the following indicators:

- indicator 1: proportion of patients treated with drugs for osteoporosis combining Vitamin D (Vitamin D in Note 79, appropriate use);
- indicator 2: proportion of patients treated with Vitamin D without established hypovitaminosis in the last 12 months (Vitamin D out of Note 96, inappropriate use).

In the 12 months pre- and post-Note 96, the calculation of indicator 1, which measures adherence to the reimbursement criteria in Note 79, showed a reduction in the proportion of patients who combine Vitamin D with osteoporosis drugs, from 70.2% to 60.4% of the total number treated with osteoporosis drugs, as shown in Figure 1.

Conversely, no appreciable differences were found in the calculation of indicator 2, which measured the deviation from the reimburse-

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Conflict of interest
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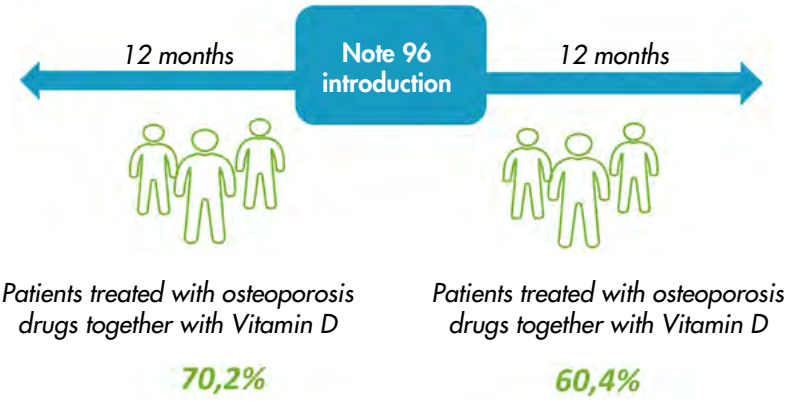

FIGURE 1.
Proportion of patients treated with osteoporosis drugs together with Vitamin D in the 12 months before and after the introduction of Note 96.

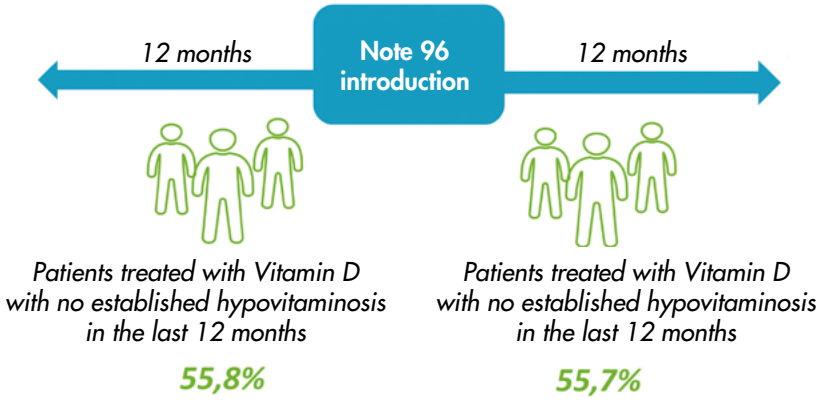

FIGURE 2.
Proportion of patients in the 12 months before and after the introduction of Note 96 treated with Vitamin D with no established hypovitaminosis in the last 12 months (excluding patients in Note 79 for whom the determination of 25(OH)D levels is not envisaged).

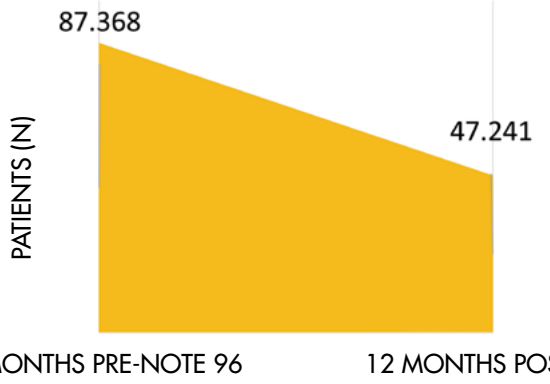

FIGURE 3.
Total number of patients treated with Vitamin D in the 12 months before and after the introduction of Note 96.

ment criteria in Note 96: the proportion of patients treated with vitamin D without ascertained hypovitaminosis in the last 12 months, excluding patients in Note 79 for whom the determination of 25(OH)D levels was not envisaged, remained unchanged (55.8% vs 55.7%), highlighting how, net of osteoporotic patients, more than half of those treated with vitamin D did not have the indications for the drugs being reimbursed (Fig. 2).

Instead, the total number of patients treated with vitamin D was significantly reduced: as illustrated by figure 3, going from 87,368 to 47,041 subjects, with a resulting drop in expenditure (-€1.1 million: -44.8%).

On the whole, the results of the analysis showed a reduction on the use of Vitamin D, determined by a lower number of patients receiving these supplements on a reimbursable basis. Nevertheless, this decrease did not coincide with an improvement in the appropriateness of prescriptions, which, in contrast, declined, especially as regards to its use in combination with osteoporosis drugs. Indeed, while the proportion of patients treated with vitamin D without 25(OH) D detection remained equally high in the two periods, the proportion of patients who combined vitamin D with osteoporosis drugs fell by 10 percentage points. This suggests the need to implement clinical practice monitoring measures to promptly identify actions that will optimise the appropriateness of prescriptions.

The literature has widely acknowledged that inadequate vitamin D supplementation in combination with anti-osteoporotic treatments can reduce the effect of these therapies and lead to an increase in adverse outcomes.[14,15] Several published studies have observed in Italian settings a greater increase in bone density and a significant decrease in fracture risk in post-menopausal women treated with osteoporosis drugs in combination with Vitamin D supplements compared to patients taking only anti-osteoporotic therapies.[14] In addition, a previous retrospective observational study, based on administrative databases from a sample of Local Health Services, conducted on a cohort of osteoporotic patients with a previous fragility fracture, showed a lower incidence rate of re-fracture among patients on calcium/Vitamin D supplementation than among those receiving either osteoporosis medication alone or no treatment for the condition.[16] Moreover, patients receiving calcium/vitamin D supplementation in addition to osteoporosis medication had a 64% reduced risk of developing a subsequent fracture and two times less risk of death compared to the group receiving osteoporosis medication alone.[16] In line clinical outcomes, costs for clinical care for osteoporotic patients receiving calcium/Vitamin D supplementation

were also lower.[17] On the other hand, supplemental vitamin D in situations other than osteoporotic fracture prevention is one of the most hotly debated issues in the medical field, being a source of controversy and beliefs that can also be strongly antithetical. Numerous observational studies of various pathological situations (heart disease, neoplasia, degenerative diseases, respiratory metabolic diseases etc.) have indicated that general health conditions in populations with low vitamin D levels are poor.[18]

However, the results of large-scale randomised clinical trials have not confirmed these hypotheses whilst revealing areas of documented ineffectiveness of vitamin D supplementation, especially in oncology and cardiology. The scientific literature considers a 25(OH)D value of 20 ng/mL (50 nmol/L) to be the limit beyond which adequate intestinal absorption of calcium and control of parathormone levels can be ensured in nearly the entire population. For this reason, it represents the level below which supplementation should be started.

Ultimately, as summarised by the two AIFA Notes, the literature has emphasised the importance of ensuring adequate vitamin D supplementation to prevent osteoporotic fragility fractures, to decrease the incidence of such events, as well as to limit the onerous economic burden associated with them, and that vitamin D should be supplemented in the presence of 25(OH)D values >20 ng/mL in osteoporotic patients.

On this basis, the analysis conducted clearly indicates the need for the appropriateness of vitamin D use to be optimised both for osteoporotic patients per Note 79, for whom vitamin D should be more widely prescribed, and in presumed deficient states, where more than 50% of patients receive supplementation without having had a 25(OH)D dosage, as provided for by Note 96.

The implementation and periodic monitoring of appropriateness indicators, designed to identify uses where there is no indication for use (vitamin D outside Note 96) and areas where there is a recommendation but no prescription (vitamin D in Note 79), offers an opportunity to organise and develop clinical governance and internal monitoring processes, to improve patient care, in the form of clinical audits within the individual local health services. Finally, the involvement of primary care general practitioners would make it possible to identify off-target patients to audit, thus aiding in the reduction of inappropriate prescriptions, resulting in improved patient health and lower healthcare resource consumption.

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