

GUIDELINE

Call to action: a five nations consensus on the use of intravenous zoledronate after hip fracture

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Abstract

Currently in the UK and Ireland, after a hip fracture most patients do not receive bone protection medication to reduce the risk of refracture. Yet randomised controlled trial data specifically examining patients with hip fracture have shown that intravenous zoledronate reduces refracture risk by a third. Despite this evidence, use of intravenous zoledronate is highly variable following a hip fracture; many hospitals are providing this treatment, whilst most are currently not. A range of clinical uncertainties, doubts over the evidence base and practical concerns are cited as reasons. This paper discusses these concerns and provides guidance from expert consensus, aiming to assist orthogeriatricians, pharmacists and health services managers establish local protocols to deliver this highly clinically and cost-effective treatment to patients before they leave hospital, in order to reduce costly re-fractures in this frail population.

Keywords: hip fracture, osteoporosis, zoledronate, secondary prevention, older people

Key Points

- Most people do not receive bone protection medication as secondary prevention after a hip fracture.
 - A quarter of people will break another bone within 5 years after a hip fracture.
 - Intravenous zoledronate can reduce the risk of refracture by a third in this population.
 - Protocols to provide this treatment before patients leave hospital should be a standard of care.
 - Common concerns about zoledronate should not prevent the development of such protocols.
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Introduction

In their *Age and Ageing* review of major changes to the National Institute of Health and Care Excellence (NICE) accredited, UK National Osteoporosis Guideline Group (NOGG) guidance in 2021, Gregson and Compston considered the implications of the new recommendations for geriatricians and orthogeriatricians and concluded that ‘there is a large treatment gap that deprives many individuals at high risk of fracture from receiving effective anti-osteoporosis treatment’ [1].

The extent of this is demonstrated by national clinical audit data. The National Hip Fracture Database (NHFD) records that in 2022, intravenous treatments were given to 21% of patients discharged following hip fracture in England, Wales and Northern Ireland [2], but this varied from 0% to 75% among hospitals (Figure 1). This increase from the mean figure of 14.4% in 2020 largely reflects an increase in patients started on intravenous zoledronate (IV Zol), from 9% in 2020 to 16% in 2022.

The NOGG recommendation for IV Zol as a first-line treatment to reduce fracture risk, especially after hip fracture, is an important potential step towards addressing this variation [3, 4]. Many hospitals have already adopted this approach, and it is now standard practice within Scotland [5]. However, the physiological heterogeneity of frail, older people who typically suffer hip fracture makes it challenging to develop simple protocols for the safe and effective delivery of IV Zol. The 2021 *Age and Ageing* review included a suggested approach, but the authors recognised the complexity underpinning each decision in a series of steps in any protocol [1]. In this paper, we consider the evidence, practicalities and some economic considerations of an approach refined by expert consensus and outline the key issues orthogeriatricians will wish to discuss with pharmacists, fracture liaison services

and patients when organising their own local hospital IV Zol pathway.

Methodology

The need for a consensus statement developed out of a recognition of the extreme variation in practice between different hospitals that has been identified by multiple national clinical audits of hip fracture: the NHFD in England, Wales and Northern Ireland [2]; the Scottish Hip Fracture Audit (SHFA) [5]; and the Irish Hip Fracture Database (IHFD) [6]. The consensus development group therefore included the orthogeriatrician clinical leads for each of these national audits and the rheumatologist lead for the Fracture Liaison Service Database (FLSDB), the audit of secondary prevention of fragility fracture in these countries [7].

This consensus paper primarily aims to provide support to the hundreds of orthogeriatricians working in multidisciplinary teams with other clinicians, surgeons, pharmacists, nurses and allied health professionals across the British Isles, including through fracture liaison services. Between them, the five orthogeriatricians on the writing group have nearly a hundred years of experience leading secondary prevention of fragility fracture in this patient group, and the first two authors alone have provided IV Zol to over 5,000 patients with hip fracture. The contrast between current clinical practice and the recommendations of the NOGG [3, 4] led to the inclusion of leading orthogeriatricians, bone specialists and rheumatologists from the NOGG, the Bone Interest Group of Scotland (BIGOS), the Wales Osteoporosis Advisory Group (WOAG) and the UK Fragility Fracture Network (FFN UK), a number of whom have personal experience of guideline development for the National Institute for Health and Care Excellence (NICE) or the Scottish

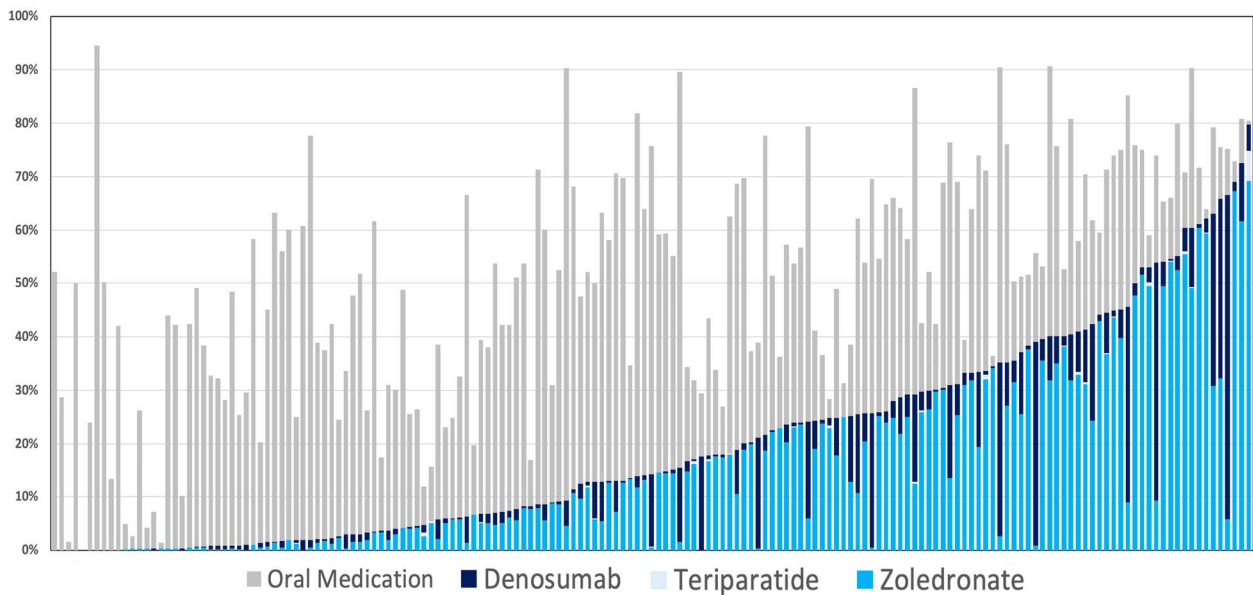


Figure 1. NHFD data on variation in bone treatments for patients discharged following presentation with a hip fracture to each of the 170 hospitals in England, Wales and Northern Ireland in 2022.

Intercollegiate Guideline Network (SIGN). All eight authors have completed and submitted the declaration of interest forms used by the NICE for its advisory committees, but have no conflict of interest, beyond their roles in these organisations. This consensus document reflects the authors' own views and not those of these organisations. Each of these organisations has formal processes for patient and public involvement (PPI), and, given the operational nature of the issues that are currently limiting IV Zol use, it was not felt beneficial to involve additional PPI in the development of this consensus statement.

The speciality of orthogeriatrics is less well developed in many countries, but the writing group included members of the Hip Fracture Audit and the Secondary Prevention advisory groups of the Global Fragility Fracture Network (FFN) [8], and this work will encourage other countries to consider how they implement effective secondary fracture prevention appropriate to their own populations and health economies.

This consensus paper was entirely unfunded; the authors did this work on a voluntary basis. The decision to write a consensus statement rather than a guideline reflected the fact that formal guidance already exists, but a series of concerns and uncertainties currently limit guideline implementation in many hospitals. As such, we would not anticipate a need to update this statement, unless new drug developments or future revisions of national guidance were to pose additional challenges to clinical teams. Notably, this statement forms the basis for planned work within the Global FFN, which may lead to a revision that takes other factors into account (including the absence of geriatricians and financial constraints) in extending this call to action to those working in other countries.

An initial scoping meeting of the writing group identified key areas of concern, drawing on prior clinical experience, expressed uncertainties received from colleagues and participants in the national audits that the writing group members were each leading. These were then drawn together into six themes. Individual members with particular clinical and/or research experience in each area then reviewed the relevant literature and drafted the introduction and each of the six sections. These sections were then reviewed by the writing group and discussed in a series of five fortnightly virtual meetings, where they were iteratively expanded, reworded and refined in content until consensus was agreed. For each section, a summary consensus statement that captured the implications of each section was agreed during these meetings, and these statements were then combined into the management flowchart (Figure 2).

Considerations when designing a protocol for IV zoledronate after a hip fracture

Vitamin D status and vitamin D loading regimes

The primary aim of vitamin D loading is to reduce the risk of symptomatic hypocalcaemia. Short-term supplementation using typical daily doses of 400–800 IU is insufficient to

achieve this. NICE guidance recommends 300,000 IU of vitamin D, split into divided doses over a 6–8-week period [9]. However, this timescale is impractical in the acute hip fracture setting, where the primary aim should be to administer the IV Zol as efficiently as is safe in a time of highly imminent re-fracture risk, i.e. prior to discharge from hospital to avoid the need to return whilst mobility is recovering.

Biochemical vitamin D deficiency is common in the hip fracture population. Checking vitamin D levels before loading can cause delay, generate inaccurate results in the acute phase and add to costs and workload. High-dose loading provides an alternative approach, with toxicity in the form of severe hypercalcaemia very rare.

Whilst large vitamin D doses given to community-dwelling, vitamin-D-replete women may paradoxically increase fracture risk (RR 1.25 for all fractures with 500,000-IU oral vitamin D3 [10]; RR 1.49 for hip fracture with 300,000-IU intramuscular vitamin D2 [11]), any risk associated with higher dosing in a community setting must be balanced against the huge potential benefit of administering IV Zol safely prior to discharge, in a hip fracture population with a high prevalence of vitamin D deficiency. In support, a single-dose 250,000 IU oral vitamin D has been shown to be safe and effective after hip fracture [12, 13]. Hence, a loading regime of 150,000–250,000 IU, given in 'split' doses over 1–7 days, is appropriate. The risk of missing a single large dose (for instance, if a patient is 'nil by mouth', delirious or vomiting or if lost tablets or spillages mean the drug is erroneously recorded as having been taken) can be minimised by 'splitting' loading doses. The prescribed vitamin D must be taken before IV Zol is administered.

If serum calcium is high on admission, high-dose vitamin D supplementation should be avoided whilst the hypercalcaemia is investigated since, rarely, vitamin D loading may unmask previously undiagnosed primary hyperparathyroidism. Patients with a baseline calcium at the upper end of normal (≥ 2.5 mmol/l) should have a follow-up serum calcium test 4–6 weeks after vitamin D loading (IV Zol administration need not wait for this follow-up test). If serum calcium is normal on admission, or initial hypocalcaemia resolves with vitamin D loading, then further testing is not needed.

Expert group consensus

Many patients with hip fracture are vitamin D deficient. If vitamin D status is unknown and the serum calcium level is normal, any risks of empirical high-dose vitamin D loading are outweighed by the benefit of allowing IV Zol to be given promptly as an inpatient. Daily oral dosing regimens to provide between 150,000 and 250,000 units over 1–7 days are appropriate.

Renal function and the safety, dose and speed of zoledronate infusions

The only randomised controlled trial to address secondary fracture prevention following hip fracture gave annual

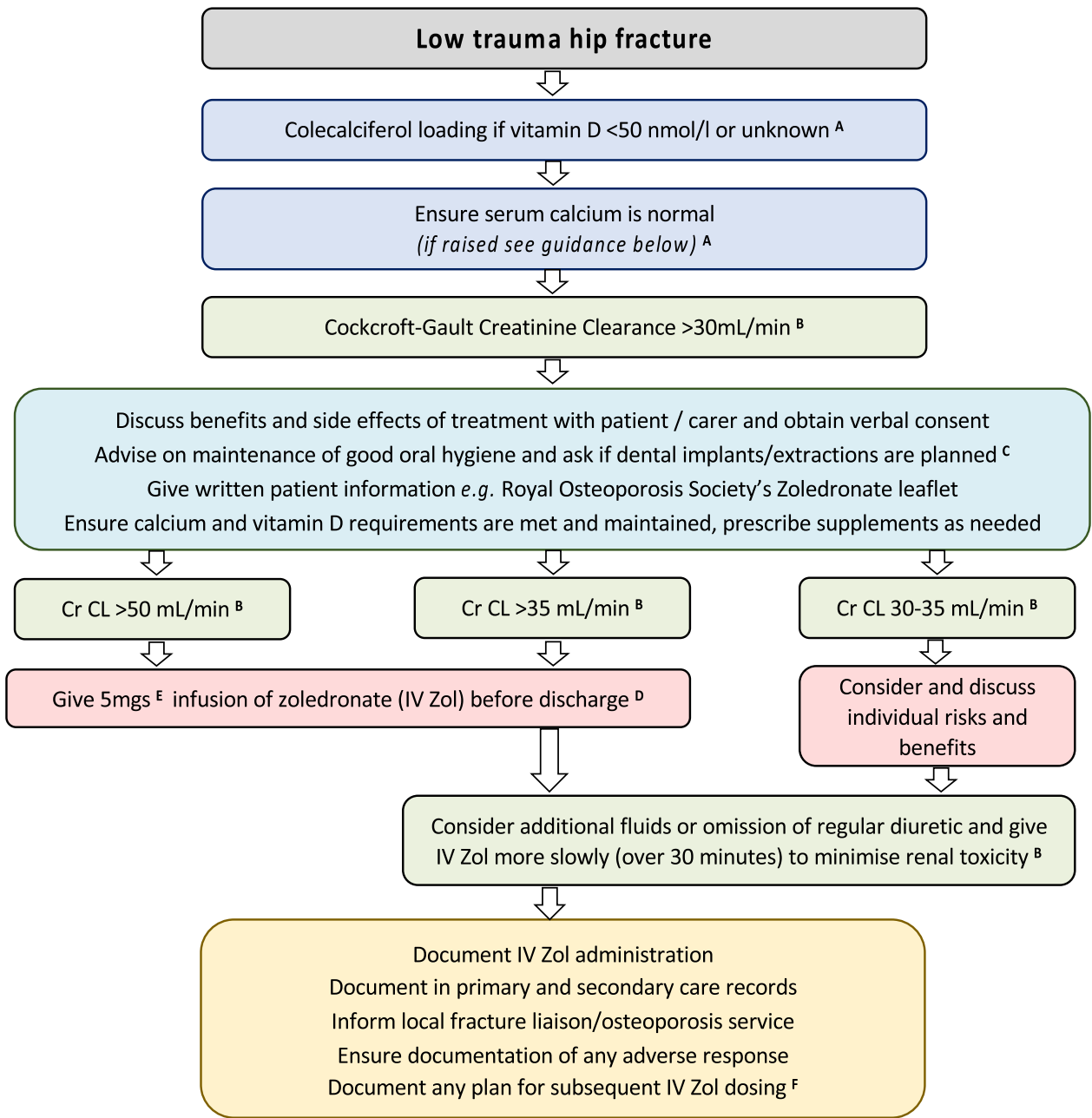


Figure 2. Flow diagram of a suggested approach to intravenous zoledronate after hip fracture A to F link to sections in the text, where each step is discussed in more detail: A: Vitamin D status and vitamin D loading regimes B: Renal function and the safety, dose, and speed of zoledronate infusions C: Dental issues and low risk of osteonecrosis of the jaw D: Timing of infusion, need to wait 2 weeks and risk of non-union E: How big a dose of IV Zol is needed? F: How often does IV Zol need to be given?

infusions of IV Zol or placebo to 2,127 women and men with a creatinine clearance (CrCl) >30 ml/min [14]. Renal adverse events were similar between groups (6.2% vs. 5.6%) in this RCT, and other work has questioned whether IV Zol has any direct acute effect on kidney function in patients with renal function in this range [15].

The Medical and Healthcare Products Regulation Agency (MHRA) recommends using CrCl to make decisions for patients age ≥ 75 years and at extremes of body weight,

acknowledging that an estimate of body weight is all that may be feasible in the acute setting [16]. Laboratory eGFR is based only on patients' age and sex and can markedly underestimate renal impairment. In one study of 163 patients with hip fracture, eGFR was on average 19 ml/min higher than CrCl calculated using the Cockcroft–Gault formula and 25 ml/min higher in people weighing <60 kg [17].

The MHRA recommends that patients should not receive 5-mg IV Zol if CrCl is below 35 ml/min [18],

the British National Formulary (BNF) states ‘avoid in treatment of postmenopausal osteoporosis and osteoporosis in men if creatinine clearance less than 35 ml/minute’ [19] and the summary of medical product characteristics (SmPC) states that IV Zol is contra-indicated with CrCl <35 ml/min [20].

However, this guidance has been questioned by a number of studies [21–23]. In a study of 558 infusions of IV Zol in 327 patients aged 75 years or older, Fixen *et al.* reported that just eight (1.4%) experienced an acute kidney injury (AKI) in the following year, with creatinine levels all returning to within 0.1 mg/dl of baseline within the year [21]. All those who experienced an AKI not only had CrCl > 45 ml/min but also had known risk factors for Zol-induced nephrotoxicity, such as concurrent nephrotoxic medication and dehydration. Twenty-five patients (4.5%) had CrCl <35 ml/min at the time of the infusion, and none of these experienced an AKI in the following year.

Schini *et al.* found treatment thresholds of eGFR >50 and CrCl >35 to be equally poor in predicting risk of AKI [22]. If MHRA advice had been followed, 996 of 7,660 infusions would not have been given because of baseline CrCl <35 ml/min. Of these 996, follow-up serum creatinine within 14 days was available on only 142 infusions (14.3%), but only four resulted in an AKI, i.e. 2.8% vs. 4.6% across all renal function ranges, for whom 14-day creatinine was available. The authors concluded that ‘eGFR is at least as good a predictor of AKI as CrCl, and permits the treatment of more patients at high fracture risk’. However, the study did not specifically consider people with hip fracture, and the mean age of 75 is lower than that of 83 years in people with hip fracture.

More recently, Sahota *et al.* gave 5-mg IV Zol over 60 min to 102 patients (mean age 88 years; 63% with hip fracture) who would not have received treatment using a CrCl threshold of ≥ 35 ml/min [23]. Their mean CrCl was 31.2 ml/min, and this remained unchanged 4 weeks later.

These studies recommended that infusions should be given over 30 min with eGFR < 50 ml/min [15, 21, 23]. Clinical data suggest that potential renal damage with IV Zol may be infusion-time-related and dose-related. Slowing infusion times from 5 to 15 min in cancer patients has improved renal safety [24, 25], and the renal drug handbook recommends slowing ibandronate infusions from 15 min down to 2 h, according to renal function [26]. When administering IV Zol, it is important to ensure that the patient is well hydrated, potentially using pre- and post-infusion oral and/or IV fluids or omitting/reducing any regular diuretics on the day.

There is currently no randomised control trial level evidence to inform the use of IV Zol in those with a CrCl between 30 and 35 ml/min, and concerns over a possible risk to renal function should be weighed against the potential benefits in terms of fracture prevention in this high-risk group. Of note, denosumab offers an alternative treatment option in those with impaired renal function.

Expert group consensus

Assessment of renal function should be based on a calculated CrCl. IV Zol should not be given when CrCl is <30 ml. Although there are few data, IV Zol appears safe when CrCl is as low as 30–35 ml/min and may be a treatment option on a case-by-case basis, with due precautions. IV Zol should be given over at least 30 min when CrCl is <50 ml/min.

Dental issues and extremely low risk of osteonecrosis of the jaw

Individuals who take anti-resorptive therapies such as IV Zol are at very low risk of developing osteonecrosis of the jaw (ONJ). ONJ is defined as exposed bone, or bone that can be probed through a fistula in the maxillofacial region, that has persisted for more than 8 weeks and without a history of radiation therapy or metastatic disease to the jaw [27]. The pathophysiology is not fully understood and is probably multifactorial. ONJ is more prevalent in patients who have procedures that have impact on bone, such as tooth extractions and possibly dental implants, but ONJ can be spontaneous. Risk factors include cumulative bisphosphonate dosage and duration of treatment [28], concurrent periodontal disease, treatment with systemic steroids and people of Asian ethnicity [29]. ONJ is also seen in people who have never used anti-resorptive therapies. The risk of ONJ is 0–2.3% with bisphosphonates for a cancer diagnosis [27]. With oral bisphosphonates for osteoporosis, the risk is 0–0.1%, but probably increases with longer therapy duration [27, 28, 30, 31]. The risk with annual IV Zol is similar: one study identifying a single case in around 6,000 patients (0.017%) [32].

In patients commencing IV Zol therapy, some consideration of dental health should be made [33]. Patients should be encouraged to seek routine dental care where possible, with the reasoning for good dental hygiene explained. However, the very low absolute risk of ONJ, particularly for those who are treatment naïve, needs to be balanced against the high absolute risk of further imminent fragility fractures. It is important not to delay treatment on dental grounds when the benefits of IV Zol outweigh the risks. Further, patients should not be declined dental treatment if need arises following IV Zol administration [33].

Expert group consensus

For patients with hip fracture, the absolute risk of imminent fragility fractures and the clear benefits of IV Zol usually far outweigh any potential risk of ONJ. Dental considerations should not limit the use of IV Zol; patients should be informed of the very rare risk of ONJ and be encouraged to maintain good oral hygiene.

Timing of infusion, no need to wait 2 weeks and risk of non-union

One-quarter of hip fracture patients re-fracture within 5 years [34]. Half of re-fractures occur within 18 months

[35], so prompt anti-osteoporosis treatment is crucial. A single IV Zol infusion reduces fracture risk by 23% (HR 0.77 [0.57–1.03]; $P = 0.080$) by 6 months [36], so clinical benefit can be achieved even in people with limited life expectancy, potentially preventing a painful death.

In 2020, the median acute length of stay for hip fracture was 15.2 days [2], so a potential barrier to pre-discharge IV Zol is the SmPC recommendation ‘to give the Aclasta infusion at least two weeks after hip fracture repair’ [20]. The evidence behind this suggested 2-week wait lies in a *post hoc* analysis of the HORIZON recurrent fracture trial [14], in which 2,127 hip fracture patients were randomised to 5 mg of IV Zol or placebo. At 12 months, total hip bone mineral density (BMD) increases were similar in all sub-groups, irrespective of infusion timing. However, the 95% confidence interval was widest, overlapping the null in the smallest sub-group (those who received IV Zol before 2 weeks). Clinical fracture risk reduction was only evident in the largest sub-group (those receiving IV Zol 4–6 weeks after surgery); in all other subgroups, the 95% confidence interval overlapped the null. Based on this, authors concluded that they had found a ‘suggestion of reduced drug efficacy in subjects dosed within 2 weeks of their fracture repair’. However, those receiving IV Zol within 2 weeks were older and more co-morbid. Serum vitamin D was not measured, but it is highly likely that this sub-group was more often vitamin D deficient and inadequately replaced with the study’s modest vitamin D doses [37]. The small sample size meant that the study was underpowered to detect an association with this relatively infrequent outcome: a classic case of ‘absence of evidence, not evidence of absence’.

Widespread subsequent experience with IV Zol between 1 and 2 weeks post-surgery shows it to be well tolerated. Infusion timing is not associated with acute-phase response [38]. Systematic reviews and meta-analyses of early post-surgery administration (10 studies, totalling 2,888 patients), show BMD gains over 12 months, with no evidence of non-union or delayed radiological or clinical fracture healing [39, 40].

Expert group consensus

Patients with hip fracture patients are at very high imminent re-fracture risk making it important that they receive IV Zol before they are discharged, so long as vitamin D replacement is complete and renal function has stabilised after surgery.

How big a dose of IV Zol is needed?

When a single dose of 1, 2.5 and 5 mg was compared, greater and longer bone suppression was seen with the higher doses [41], but IV Zol is so highly effective that at any dose, it will meet the NICE criteria for cost-effectiveness [42]. No adequately powered trial has compared BMD or clinical endpoints between 5 and 4 mg, but a small study from Japan demonstrated higher peak blood zoledronate levels and only

negligible difference in bone turnover markers with 5 mg [43].

In 2023, the British National Formulary listed the cost (excluding VAT) of a single 5-mg infusion of Aclasta at £253.38, whilst generic versions of zoledronic acid are available at £85 for 5 mg in a 100-ml bag and just £2.73 for 4 mg in a 5-ml vial [19]. In health economies where pharmacy budgets are constrained, the cost of Aclasta needs to be set against the potential benefit of giving generic zoledronic acid to many more patients.

Expert group consensus

The original trial of IV Zol after hip fracture used annual doses of 5 mg, but subsequent studies have shown similar effects on bone biochemistry with lower doses. The less expensive 4-mg formulation is an alternative if health resources are constrained or the 5-mg formulation is not accessible.

How often does IV Zol need to be given?

The HORIZON recurrent fracture trial specifically focused on patients with hip fracture [14]; three annual doses of 5 mg led to a 35% reduction in clinical fracture risk [44]. Annual 5-mg dosing for 3 years is therefore the standard regimen. The first dose of IV Zol is the most important, and a single dose may suffice for those with more severe frailty and comorbidities associated with high 1-year mortality or when the therapeutic burden of attending a clinic or other external facility to receive further IV Zol appears unrealistic. Notably, the BMD effects of a single dose of IV Zol are maintained for several years in frail nursing home residents and in postmenopausal women [45, 46]. A subgroup analysis of the two HORIZON trials showed people who received just one dose of IV Zol experienced a similar fracture risk reduction after 3 years as those who had all three [47]. Although, the subgroups were different at baseline, those who received one dose had more fracture risk factors. Given the wide confidence intervals for fracture outcomes, it cannot be concluded that a single dose is equivalent to three consecutive annual doses. The HORIZON-PFT Extension continued treatment for a further 3 years and saw a greater vertebral fracture risk reduction in those at higher fracture risk, lending weight to the benefit of repeated IV Zol [48].

Determining who should just receive a single dose is ultimately a clinician’s decision, as part of a comprehensive geriatric assessment (CGA). The NHFD’s 4-month postal or telephone follow-up is one opportunity to identify patients suitable for subsequent doses. Tools such as the Clinical Frailty Scale (CFS) can act as an adjunct in decision-making but should not be used in isolation to determine treatment decisions, particularly by non-specialists [49]. An 18- rather than 12-month dosing regimen will ease the burden on both patient and infusion services and may represent an appropriate compromise in terms of future fracture risk reduction, but this has only been tested in women at lower fracture risks [50].

Where services able to administer repeated IV Zol are lacking, efforts should be made to set these up. Innovation is needed to ‘de-centralise’ IV Zol services, to enable greater, more equitable access to treatments through community hospitals, GP practices, ‘hospital-at-home’ and ‘home IV’ services, to mitigate against the difficulties of relying on hospital-based infusion services. Home-based infusion services providing IV Zol have been piloted successfully in one NHS centre in Nottingham [51]. Another option is to switch patients to denosumab 1 year after their zoledronate dose if renal deterioration precludes further zoledronate and the patient remains at high fracture risk.

Expert group consensus

The first dose of IV Zol is the most important to offer to inpatients. Further doses at 12–18-month intervals carry additional benefit and should be arranged, unless individual patients’ frailty at the time of discharge suggests that this will not be beneficial or feasible. Local community services need to innovate to enable practical solutions to subsequent dosing.

Discussion

This paper is not intended as a guideline, but is a response to guidance already published by the NOGG and the Bone Interest Group of Scotland, given the huge variation in practice that is apparent across the British Isles. Our writing group did not use formal methods to reach consensus, but brought together very extensive personal experience in using IV Zol in this very high-risk patient group, the unique insight of those leading national audit across these five countries and the expertise of specialists in clinical osteoporosis management and research.

Our work highlights key future research questions, including the clinical efficacy of the 4- and 5-mg formulations, the use of one or three doses in frail older people with hip fracture and the need to confirm the long-term renal safety among people with CrCl in the 30–35-ml/min range. In clinical practice, a wider range of treatment options are available, including oral bisphosphonates such as denosumab and anabolic agents such as romosozumab, but we suggest that the success of any treatment strategy in reducing re-fracture rates will depend on how effectively hospital teams organise their provision of IV Zol as a first-line treatment option.

This work is orientated towards improving clinical services in the British Isles and will be disseminated through webinars and the reporting of national clinical audits: the NHFD in England, Wales and Northern Ireland, the SHFA and the IHFD and the FLS-DB. The origin of this work in these national audits means hospital teams will be able to use the audits to demonstrate the impact of changes in practice in response to this consensus statement. This consensus will be the focus for an international workshop at the Global IFFN meeting in 2023, where the implications of different

regulatory frameworks, different models of IV Zol delivery and different financial considerations in other countries can be discussed.

Conclusion—a ‘call to action’

A quarter of people will die in the year following hip fracture, and competing mortality may encourage clinicians to accept lower osteoporosis treatment rates, particularly in older, frailer adults. However, frailty is also a strong predictor of fracture risk, and re-fracture is common in the first year. IV Zol begins to lower re-fracture risk after 6 months, reducing the risk of a further painful and debilitating admission. IV Zol is a highly cost-effective, first-line anti-osteoporosis treatment. We invite all those looking after patients with hip fracture to ask not ‘should I give IV Zol?’, but ‘why wouldn’t I give IV Zol?’, and to set up pragmatic local pathways of care to effect this best practice.

Declaration of Conflicts of Interest: All eight authors have completed and submitted the declaration of interest forms used by NICE for its advisory committees. These identify that M.K.J. is an advisory group member, that O.S. and M.K.J. have received speaker fees, that M.K.J. has received institutional grant funding, and consultancy fees and that A.J.B. and M.K.J. have received support for conference registration, accommodation and travel from various drug companies. However, none of these companies are the manufacturers of Aclasta or of generic forms of zoledronate. The authors’ other declarations, of non-financial, professional or personal interest reflect their voluntary roles in the national and international organisation that are described in the [Methodology](#) section; including A.J., A.M. and E.A.’s roles as leads of the hip fracture audits for the five nations of the British Isles.

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