GUIDELINES

Risk assessment of fragility fractures: summary of NICE guidance

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This is one of a series of *BMJ* summaries of new guidelines based on the best available evidence; they highlight important recommendations for clinical practice, especially where uncertainty or controversy exists.

Further information about the guidance, a list of members of the guideline development group, and the supporting evidence statements are in the full version on bmj.com.

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Previous articles in this series

- Risk assessment of fragility fractures: summary of NICE guidance (*BMJ* 2012;345:e3698)
- Risk identification and interventions to prevent type 2 diabetes in adults at high risk: summary of NICE guidance (*BMJ* 2012;344:e4624)
- Management of an acute painful sickle cell episode in hospital: summary of NICE guidance (*BMJ* 2012;344:e4063)
- Management of venous thromboembolic diseases and the role of thrombophilia testing (*BMJ* 2012;344:e3979)
- Recognition, referral, diagnosis, and management of adults with autism (*BMJ* 2012;344:e4082)

Osteoporosis is characterised by low bone mass and structural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture, particularly fractures that result from mechanical forces that would not ordinarily result in fracture, known as fragility fractures. The prevalence of osteoporosis rises markedly with age, and in women this rises from 2% at 50 years to more than 25% at 80 years. Risk of fracture is also increased by factors such as lifestyle, drug treatments, family history, and other conditions that cause secondary osteoporosis. Several validated risk assessment tools are available to predict fracture risk. This article summarises the most recent recommendations from the National Institute for Health and Clinical Excellence (NICE) on risk assessment of fragility fractures.[1]

Recommendations

NICE recommendations are based on systematic reviews of the best available evidence and explicit consideration of cost effectiveness. When minimal evidence is available, recommendations are based on the Guideline Development Group's experience and opinion of what constitutes good practice. Evidence levels for the recommendations are in the full version of this article on bmj.com.

Box 1 | Main causes of secondary osteoporosis

Endocrine—Hypogonadism in either sex including untreated premature menopause and treatment with aromatase inhibitors or androgen deprivation therapy; hyperthyroidism; hyperparathyroidism; hyperprolactinaemia; Cushing's disease; diabetes

Gastrointestinal—Coeliac disease; inflammatory bowel disease; chronic liver disease; chronic pancreatitis; other causes of malabsorption

Rheumatological—Rheumatoid arthritis; other inflammatory arthropathies

Haematological—Multiple myeloma; haemoglobinopathies; systemic mastocytosis

Respiratory—Cystic fibrosis; chronic obstructive pulmonary disease

Metabolic—Homocystinuria

Renal—Chronic renal disease

Immobility—Resulting, for example, from neurological injury or disease

Box 2 | Risk assessment tools

FRAX (www.shef.ac.uk/FRAX), the World Health Organization's fracture risk assessment tool can be used for people aged 40-90 years, with or without values for bone mineral density

QFracture (www.qfracture.org/index.php) can be used for people aged 30-85 years of age. Values for bone mineral density cannot be incorporated into the risk algorithm

Who needs risk assessment?

- Consider assessing fracture risk in:
  - All women aged ≥65 years and men aged ≥75.
  - Women between 50 and 65 years and men between 50 and 75 years if they have risk factors—for example, previous fragility fracture; history of falls; current or frequent recent use of oral or systemic glucocorticoids; other causes of secondary osteoporosis (box 1); smoking; alcohol intake >14 units a week for women and >21 units a week for men; family history of hip fracture; low body mass index (kg/m^2) (<18.5).
- People aged <50 years are unlikely to be at high risk of fracture, so do not routinely assess their fracture risk with a risk assessment tool unless they have major risk factors (for example, current or frequent recent use of oral or systemic glucocorticoids, untreated premature menopause, or previous fragility fracture).
- In people aged <40 years, consider measuring bone mineral density to assess their fracture risk only if they have a major risk factor such as history of multiple fragility fractures, major osteoporotic fracture, or current or recent use of high dose oral or high dose systemic glucocorticoids (>7.5 mg prednisolone or equivalent daily for three months or longer).
- Consider to be at high risk people over the age limit of the risk assessment tools (90 years for FRAX and 85 years for QFracture; box 2).

How to carry out risk assessment

- Estimate the absolute risk of fragility fracture—for example, the predicted risk of major osteoporotic or hip fracture over 10 years, expressed as percentage.
- Use FRAX (without a value for bone mineral density) or QFracture, within these tools' allowed age range, to estimate absolute risk of fracture.
- If, after such risk assessment, the fracture risk is in the region of an intervention threshold for a proposed treatment, consider measuring bone mineral density with dual energy x ray absorptiometry (DXA), and recalculate the absolute risk by using FRAX again but this time incorporating the value for bone mineral density. (The guideline does not provide advice on what level of risk merits consideration of intervention. NICE will not be able to recommend drug interventions until its current technology appraisals dealing with drug interventions for reduced bone mineral density are updated.)
- Consider measuring bone density with DXA before starting treatments that may rapidly adversely affect bone mineral density—for example, sex hormone deprivation for breast or prostate cancer.

Be aware

- Risk assessment tools may underestimate fracture risk in certain circumstances—for example, when a patient has a history of multiple fractures; has had previous vertebral fracture(s); has a high alcohol intake; has had high dose oral or high dose systemic glucocorticoids (>7.5 mg prednisolone or equivalent) daily for three months or longer; or has other causes of secondary osteoporosis.
- Fracture risk may be affected by factors that might not be included in the risk tool—for example, living in a care home or taking drugs that may impair bone metabolism (such as anticonvulsants, selective serotonin reuptake inhibitors, thiazolidinediones, proton pump inhibitors, and antiretroviral drugs).

When to repeat risk assessment

- Consider recalculating fracture risk if *(a)* the original calculated risk was in the region of the intervention threshold for a proposed treatment and only after a minimum of two years; or *(b)* the person's risk factors have changed.

Overcoming barriers

Implementation of the guideline will require a change in approach to use absolute risk rather than measures of bone mineral density when considering risk assessment. Healthcare professionals do not routinely consider risk of fragility fracture when they see people opportunistically, and the recommendations are likely to result in a larger number of people being assessed by general practitioners (or other healthcare professionals in different settings), potentially either increasing the duration of a consultation or resulting in an additional consultation. There should, however, be a reduction in inappropriate referrals for measurement of bone mineral density.

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Competing interests: All authors were members of the Guideline Development Group for the NICE guideline; no authors have relationships with any companies that might have an interest in the submitted work in the previous three years; and no authors have non-financial interests that may be relevant to the submitted work.

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1 National Institute for Health and Clinical Excellence. Osteoporosis: assessing the risk of fragility fracture. (Clinical guideline 146.) 2012. www.nice.org.uk/CG146.

THERAPEUTICS

Bisphosphonates in the treatment of osteoporosis

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This is one of a series of occasional articles on therapeutics for common or serious conditions, covering new drugs and old drugs with important new indications or concerns. The series advisers are Robin Ferner, honorary professor of clinical pharmacology, University of Birmingham and Birmingham City Hospital, and Albert Ferro, professor of cardiovascular clinical pharmacology, King's College London. To suggest a topic for this series, please email us at practice@bmj.com.

A 74 year old woman is admitted to hospital with a subtrochanteric hip fracture after a fall in her home. The T score for the bone mineral density (BMD) in her femoral neck is −3.2. She had a wrist fracture seven years ago but is otherwise healthy. Her 10 year absolute risk of any major osteoporotic fracture is 23% (calculated with the online WHO FRAX tool, www.shef.ac.uk/FRAX). The patient is treated surgically with internal fixation of the fracture. She is advised that she has a high risk of having further fractures, and the benefits and risks of possible treatment options to reduce this risk are discussed using a decision aid (http://musculoskeletal.cochrane.org/decision-aids). It is agreed that she will take alendronate, 70 mg once weekly for five years.

What are bisphosphonates?

Bisphosphonates are analogues of inorganic pyrophosphate. They inhibit bone resorption by inducing apoptosis of osteoclasts,[1] thus preventing age related bone loss and deterioration of bone microarchitecture. Bisphosphonates that contain nitrogen (such as alendronate, risedronate, ibandronate, and zoledronic acid) have the most potent antiresorptive properties and are the most commonly used drugs in the treatment of osteoporosis. The bisphosphonate etidronate does not contain nitrogen, and although it is approved for treatment of postmenopausal osteoporosis, the evidence base is weaker and it is rarely prescribed nowadays.

How well do bisphosphonates work?

Large phase III randomised controlled trials in postmenopausal women with osteoporosis have shown significant reduction in vertebral fractures after three years of treatment with alendronate,[2] risedronate,[3 4] ibandronate,[5] and zoledronic acid,[6] and in non-vertebral fractures and hip fractures with alendronate,[2] risedronate,[7] and zoledronic acid.[6] In the Fracture Intervention Trial, the incidence of vertebral fracture in women treated for three years with alendronate 5 mg daily for 24 months followed by 10 mg daily for 12 months was 8%, compared with 15% in the placebo group (P=0.001); corresponding figures for hip fracture were 1.1% and 2.1% (P=0.05).[2] In women treated for three years with zoledronic acid, 5 mg once yearly, the incidence of vertebral fractures was 3.3% compared with 10.9% in the placebo group (P<0.001) and of hip fractures was 1.4% compared with 2.5% (P<0.001).[6] Retrospective subgroup analyses have also shown a reduction in non-vertebral fracture with ibandronate.[8] The trials in men at increased risk of fracture and in individuals taking glucocorticoids were not designed to show fracture reduction, but alendronate, risedronate, and zoledronic acid have similar effects on BMD to those observed in postmenopausal women. Calcium and vitamin D supplements were given in all the trials.

Direct comparison of the efficacy of different bisphosphonates in reducing fractures is not possible, as trial populations and designs in pivotal clinical trials have differed and head to head studies with fracture as the primary endpoint have not been performed. Comparison between bisphosphonates of the number needed to treat to prevent a fracture is unreliable because of the dependence of this estimate on the underlying risk of the trial population, which differs between studies and is an important determinant of absolute risk reduction with treatment.

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Previous articles in this series

- Carbapenem antibiotics for serious infections (*BMJ* 2012;344:e3236)
- Cholinesterase inhibitors and memantine for symptomatic treatment of dementia (*BMJ* 2012;344:e2986)
- Antimuscarinic drugs to treat overactive bladder (*BMJ* 2012;344:e2130)
- Hormone replacement therapy (*BMJ* 2012;344:e763)
- Newer drugs for focal epilepsy in adults (*BMJ* 2012;344:e345)

- Visit BMJ Group's Rheumatology portal http://www.bmj.com/specialties/rheumatology

However, on the basis of clinical trial data for alendronate and zoledronic acid, the estimated numbers needed to treat for postmenopausal women with a vertebral fracture and/or a BMD T score ≤−2.5 were 90 for hip fracture, 25 for any non-vertebral fracture (including hip), and 14 for vertebral fracture over three years.[9]

Both the National Institute for Health and Clinical Excellence (NICE) and the UK National Osteoporosis Guideline Group recommend alendronate as the first line treatment option for primary or secondary prevention of fracture in postmenopausal women.[10-12] NICE recommends etidronate or risedronate as second line options in women who cannot take or tolerate alendronate but has not conducted an appraisal of ibandronate or zoledronate. The National Osteoporosis Guideline Group considers risedronate, ibandronate, and zoledronic acid to be second line agents.

How safe are bisphosphonates?

Gastrointestinal adverse effects (including oesophagitis, gastritis, dyspepsia, oesophageal reflux, nausea, abdominal pain, and diarrhoea) may occur in patients taking oral bisphosphonates. Although in most clinical trials these were not significantly more common in treated patients than in placebo patients, post-marketing studies indicate that some increase in risk exists, particularly if the dosing instructions are not followed correctly (see box on tips for patients).[13] Musculoskeletal pain, rash, and headache occur with a frequency of ≥1/100, <1/10) and ocular inflammation (uveitis and iritis) rarely occurs (≥1/10 000, <1/1000).

Osteonecrosis of the jaw has been reported in patients taking bisphosphonates, mainly in patients with cancer who are receiving higher doses than those used for osteoporosis. A causal association with bisphosphonates has not been shown and the condition is very rare in patients with osteoporosis (incidence estimated at between 1/10 000 and 1/100 000 patient years).[14]

Atypical subtrochanteric and diaphyseal femoral fractures have also been described in patients treated with bisphosphonates for osteoporosis.[15 16] They occur after minimal or no trauma, are often associated with prodromal pain, heal poorly, and are bilateral in nearly half of cases. They are rare, accounting for about 1% of all hip and femoral fractures; the estimated incidence being 5/10 000 per year of bisphosphonate use.[17] Radiologically, atypical subtrochanteric and diaphyseal femoral fractures present as short oblique or transverse fractures, sometimes progressing from a stress fracture in the lateral cortex.

Concerns about a possible increased risk of atrial fibrillation and oesophageal cancer in patients taking bisphosphonates have been raised, but the evidence is inconclusive.

What are the precautions?

Oral bisphosphonates are very poorly absorbed (usually <1% absorption) and may cause oesophageal irritation if in prolonged contact with the oesophageal mucosa. Do not prescribe bisphosphonates if any of the following conditions apply:

- Delayed oesophageal emptying owing to oesophageal abnormalities such as achalasia or stricture (caution applies to oral bisphosphonates only)
- Inability to stand or sit upright for at least 30-60 minutes after taking the medication (caution applies to oral bisphosphonates only)
- Hypocalcaemia—correct this before starting oral or intravenous treatment
- Pregnancy or lactation
- Severe renal impairment (creatinine clearance ≤30 mL/min for risedronate and ibandronate and ≤35 mL/min for alendronate and zoledronic acid). Renal impairment has been observed after the administration of zoledronic acid, especially in patients with pre-existing renal dysfunction
- Hypersensitivity to bisphosphonates or any of the excipients.

Use caution in prescribing oral bisphosphonates to patients with active or recent oesophageal or upper gastrointestinal problems. In patients with known Barrett's oesophagus consider the benefits and potential risks of alendronate on an individual patient basis.

Administration of intravenous bisphosphonates may be associated with a self limiting influenza-like illness with fever, myalgia, arthralgia, and headache in ≥1/10 of patients.[6] To reduce the incidence and severity of these symptoms, advise taking paracetamol or ibuprofen shortly after administration of the drug.

Patients with poor oral health who need dental extraction or other invasive dental procedures are at increased risk of osteonecrosis of the jaw, so refer these patients for expert dental assessment and treatment before starting bisphosphonates and, if possible, avoid invasive dental procedures in patients already taking bisphosphonates. Advise patients taking bisphosphonates to maintain good dental hygiene.

As patients taking bisphosphonates may rarely develop atypical fractures, consider imaging in those who develop hip, thigh, or groin pain. In the patients with a diagnosis of an atypical fracture, consider imaging of the contralateral femur. Withdrawal of bisphosphonate treatment is advised in patients who develop osteonecrosis of the jaw or atypical fractures.

How cost effective are bisphosphonates?

Generic formulations of alendronate are now predominantly used (with a current NHS cost of £17.04 (€21; $27) a year). The cost effectiveness analysis conducted by NICE was conducted when the annual price of alendronate was higher (£53.56) but showed its cost effectiveness in the secondary prevention of fracture in post-menopausal women aged ≥55 years with osteoporosis and in women aged 50-55 years in whom independent clinical risk factors for fracture were also present (incremental cost effectiveness ratio (ICER) <£30 000 per quality adjusted life year).[10] For primary prevention, with an ICER of £20 000 per quality adjusted life year as the threshold, additional risk factors and/or lower BMD were needed, depending on age.[11] The analysis conducted by the National Osteoporosis Guideline Group showed that alendronate at a cost of £90 a year was cost effective in primary or secondary prevention of fracture in post-menopausal women with osteoporosis at any age and in women with a previous fragility fracture, regardless of BMD (ICER <£20 000 per quality adjusted life year).[18]

TIPS FOR PRESCRIBERS

Do not prescribe oral bisphosphonates in patients with severe oesophageal disease or in those unable to comply with the dosing instructions

Oral bisphosphonates are poorly absorbed and may cause oesophageal irritation, requiring patients to follow the administration instructions

Treatment for osteoporosis should include not only drug treatment but also advice on lifestyle, nutrition, exercise, and measures to reduce falls. Ensure adequate calcium intake and vitamin D status, prescribing supplements if needed

Encourage patients to report adverse effects such as gastrointestinal intolerance with oral agents as parenteral alternatives are available

As rare adverse effects are possible in long term users, after five years re-evaluate the need for continued treatment. Consider a "drug holiday" for two to three years unless fracture has occurred during treatment or bone mineral density remains low

TIPS FOR PATIENTS

Bisphosphonates are used in the treatment of osteoporosis to reduce the risk of having a fracture. They are given by mouth (once weekly or once monthly) or by injection (once every three months or once yearly). Calcium and vitamin D supplements are usually needed as well

When taken by mouth, the bisphosphonate tablet is taken first thing in the morning on an empty stomach with a large glass of water. You should be sitting upright or standing when you take the tablet and must not lie down for at least 30 minutes afterwards (or 60 minutes if you're taking ibandronate). No food, drink or other tablets should be taken during this time

The most common side effects with bisphosphonate tablets are indigestion and heartburn. These are less likely to occur when the tablet is taken correctly, but if they occur you should contact your GP

Some people get a flu-like illness when bisphosphonates are given by injection. This usually lasts two to three days. A mild pain reliever such as ibuprofen or paracetamol can reduce this side effect

Very rarely, a condition called osteonecrosis of the jaw may develop in people taking bisphosphonates. Before starting treatment, tell your doctor if you have problems with your teeth or gums. During treatment, have regular dental check-ups and let your dentist know that you are taking a bisphosphonate

If you develop hip, thigh or groin pain, see your doctor because, rarely, unusual fractures of the thigh bone develop in people taking bisphosphonates and an x ray may be indicated

Bisphosphonates are usually given for three to five years in the first instance. After this time your doctor may do some tests to see if you need to continue or if you can stop the treatment for two to three years. It is very important to take the treatment regularly, and if for any reason you are unable to do this, you should contact your GP

Generic versions of risedronate are also now available, although they are currently more expensive than alendronate (NHS price £19.51 a month).

How are bisphosphonates taken and monitored?

Ensure there are no contraindications to starting bisphosphonates. Assess renal function and measure serum calcium concentration (and correct any existing hypocalcaemia) before starting oral or intravenous bisphosphonate treatment. Check serum 25-hydroxyvitamin D concentrations in patients at risk of vitamin D deficiency (for example, if exposure to sunlight is low and in patients with malabsorption). Treatment for osteoporosis should include advice on lifestyle, nutrition, exercise, and measures to reduce falls. Coprescribe calcium and vitamin D supplements with bisphosphonates unless there is evidence of adequate dietary calcium intake and normal vitamin D status.

Alendronate and risedronate are taken orally and are available in once daily or once weekly formulations. Ibandronate may be taken orally as a once monthly dose or given as an intravenous injection once every three months. Zoledronic acid is given as an intravenous infusion once yearly.

As oral bisphosphonates may cause oesophageal irritation, advise patients to take the tablets on waking, with a large glass of water, and to sit upright or stand while taking the tablet and not to lie down for at least 30 minutes (alendronate and risedronate) or 60 minutes (ibandronate) after taking it. No food, drink, or other medications should be taken during this time.

Measurement of BMD is most commonly used to monitor bisphosphonate treatment. Some guidelines recommend measurement of BMD at intervals of one year or two years, although the value of this is uncertain and it may be sufficient to measure BMD after three to five years of treatment. If the patient's BMD remains low and/or fracture has occurred during treatment, continue bisphosphonate treatment, but in other patients consider a "drug holiday" for two to three years.[19 20]

If one or more fractures occur during treatment, check compliance and exclude secondary causes of osteoporosis. However, no treatment completely prevents fracture, so a fracture during treatment does not necessarily mean lack of response.

How do bisphosphonates compare with other drugs?

Other drugs approved for osteoporosis include denosumab, parathyroid hormone peptides, raloxifene, and strontium ranelate.

All these drugs reduce vertebral fractures, but only denosumab and strontium ranelate reduce non-vertebral fractures, including hip fractures. The National Osteoporosis Guideline Group considers denosumab, raloxifene, and strontium ranelate as second line agents for primary or secondary prevention of fracture in postmenopausal women.[12]

Denosumab is administered once every six months by subcutaneous injection. Strontium ranelate and raloxifene are taken orally once daily. Parathyroid hormone peptides are administered by daily subcutaneous injections.

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Patient consent not required (patient anonymised, dead, or hypothetical).

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Corrections and clarifications

For how much longer will we tolerate commercial screening?

Owing to an editorial error we misspelt the author's name in this Letter (*BMJ* 2012;344:e2729, print publication 21 Apr, p 31). It should have been David J Nicholl [not Nichol].

Investing in new services is key

An editing error occurred in this Letter by Claire Hilton (*BMJ* 2012;344:e2746, print publication 21 Apr, pp 28-9). The last sentence of the third paragraph should read: "The plan to encourage the creation of 20 'dementia friendly communities,' where individuals, businesses, and the state work together to support people with dementia seems yet another way to move government health service provision on to the communities [not "into the community"]."

Andrew Dennis Smalley

This Obituary (*BMJ* 2012;344:e2062, print publication 21 Apr, p 37) incorrectly recorded Andrew Dennis Smalley's date of qualification as 1977. He qualified from Guy's in 1987.

Asthma in elite athletes: What can we learn?

This Feature by Sophie Arie (*BMJ* 2012;344:e2556, print publication 28 Apr, pp 20-2) incorrectly stated that asthma is not a "life threatening" condition.

Diabetes drug should be removed from market, says consumer group

A few errors made it into this News story by Jeanne Lenzer (*BMJ* 2012;344:e3259, print publication 12 May, p 5). In the second paragraph it should have read that "Public Citizen's Health Research Group said that liraglutide is associated with higher than expected risks [not rates] of pancreatitis, thyroid cancer, and kidney failure." In the fourth paragraph the last sentence should have been: "The FDA [not she] also cited concerns about possible associations with thyroid and pancreatic cancer, kidney failure, and serious allergic reactions." Lastly, Sidney Wolfe's comment that was quoted in the penultimate paragraph as "Novo Nordisk's ads make Victoza sound like it's a piece of cake since you can inject once a day instead of twice daily with insulin" should have been "Novo Nordisk's ads make Victoza sound like it's a piece of cake since you can inject just once a day."

Mark Britnell: "I've got every intention of returning to the NHS"

In this Feature by Rebecca Coombes (*BMJ* 2012;344:e3239, print publication 12 May, p 22) we wrongly implied that the Framework for Securing External Support for Commissioners resulted from Mark Britnell's policy to encourage more private sector involvement in healthcare. However, the framework was established before Britnell joined the Department of Health.

David Morrell

This Obituary for David Morrell (*BMJ* 2012;344:e3227, print publication 12 May, p 36) incorrectly stated that the MSc starting in 1986 at London was the first in general practice. In fact, the first such MSc started at Glasgow in 1982, followed by those at Exeter and Leeds in 1983. The Exeter MSc was the first to be multidisciplinary.

Full results on risks of epoetin emerge 14 years after study

This News story by Keith Epstein (*BMJ* 2012;344:e3535, print publication 26 May, pp 2-3) incorrectly stated that the normal haematocrit trial "formed the basis for regulatory approval" of the drug epoetin alfa. In fact, epoetin alfa had already been approved for use in the US.

Ultrasound guided corticosteroid injection for plantar fasciitis: randomised controlled trial

In the print version of this Research paper by Andrew M McMillan and colleagues (*BMJ* 2012;344:e3260, print publication 2 Jun, p 17) pain scores in the figure should be measured as mean (SE) [not mean (SD)].

Beware renal adverse effects

During the editing of this Letter (*BMJ* 2012;344:e3838, print publication 9 Jun, pp 26-7) we inadvertently deleted the number of patients (50, as stated in the original rapid response) who developed renal thrombotic microangiopathy after taking vascular endothelial growth factor (VEGF) inhibitors. The fourth sentence in the second paragraph should have read: "Since 2005, we have identified 50 patients who developed renal thrombotic microangiopathy (small vessel injury) after taking VEGF inhibitors; 23 cases were related to intravenous bevacizumab and one followed intraocular administration of ranibizumab."