GUIDELINES

Control of pain in adults with cancer: summary of SIGN guidelines

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This is one of a series of *BMJ* summaries of new guidelines, which are based on the best available evidence; they highlight important recommendations for clinical practice, especially where uncertainty or controversy exists. Further information about the guidance and a list of the members of the development group are in the full version on bmj.com

Why read this summary?

About a third of patients with cancer report pain, rising to three quarters in the advanced stages of the disease.[1] Cancer pain has many dimensions including psychological, physical, social, and spiritual, which must be addressed in order to improve quality of life and functional ability. Surveys show that the effectiveness of pain control in patients with cancer varies, with 12% to 51% of patients reporting unsatisfactory pain control.[2,3] This article summarises the most recent recommendations from the Scottish Intercollegiate Guidelines Network (SIGN) on the control of pain in adults with cancer.[4]

Recommendations

SIGN recommendations are based on systematic reviews of best available evidence. The strength of the evidence is graded as A, B, C, or D (fig 1), but the grading does not reflect the clinical importance of the recommendations. Recommended best practice ("good practice points") based on the clinical experience of the guideline development group is also indicated (as GPP).

Factors affecting patients

- Good communication between health professionals, patients, and carers is important for accurately assessing pain and improving compliance with treatment (GPP).
- Cancer can destabilise patients' lives in terms of their self identity, belief systems, and place in the world. Health professionals should have skills to help patients deal with this spiritual pain (GPP).

Psychosocial factors

Psychological factors can profoundly influence the perception of pain and how the patient responds behaviourally and emotionally. The meaning of pain for patients with cancer may differ from that for patients with non-life threatening illness. Some patients with cancer may see increased pain as a sign of disease progression or the failure of strong medication, and this may affect mood and adherence to treatment protocols.

- In a comprehensive chronic pain assessment, include routine screening for psychological distress using a validated tool such as the brief pain inventory[5] or the hospital anxiety and depression scale (B).[6]
- Consider cognitive behaviour therapy as part of a comprehensive treatment programme for those with cancer related pain and resulting distress and disability (A).

Assessment of pain

Consider the following domains in a comprehensive assessment of pain: physical effects and manifestations of pain; functional effects; psychosocial factors; and spiritual aspects.

Why assess and who should assess?

An accurate assessment to determine the cause, type and severity of pain, and its effect on the patient will determine the most appropriate treatment (D). The patient should be the prime assessor of his or her pain (D).

How should the assessment be done?

- Assess pain by history taking, physical examination, use of standardised assessment tools (visual analogue scales, numerical rating scales, or verbal rating scales)[7] and other appropriate investigations (D).
- Use an observational pain rating scale in patients with cognitive impairment who are unable to use a self assessment pain scale (C).[8,9]
- Assess pain regularly (at least daily when pain is not adequately controlled) (GPP).

Principles of pain management

- Provide patients with information and instruction about pain and pain management, and encourage them to take an active role in their pain management (B).
- Start treatment at the step of the World Health Organization's analgesic "ladder" (fig 2) that is appropriate for the severity of the pain (B).[10]
- Always adjust prescribing of analgesia as the pain severity alters (B).

The grade of recommendation relates to the strength of the supporting evidence on which the evidence is based. It does not reflect the clinical importance of the recommendation

A	• At least one high quality meta-analysis, systematic review of randomised controlled trials, or randomised controlled trial with a very low risk of bias and directly applicable to the target population; or • A body of evidence consisting principally of well conducted meta-analyses, systematic reviews of randomised controlled trials, or randomised controlled trials with a low risk of bias directly applicable to the target population, and demonstrating overall consistency of results
B	• A body of evidence including studies rated as high quality systematic reviews of case-control or cohort studies, and high quality case-control or cohort studies with a very low risk of confounding or bias and a high probability that the relation is causal and which are directly applicable to the target population, and with overall consistency of results; or • Extrapolated evidence from studies described in A
C	• A body of evidence including well conducted case-control or cohort studies with a low risk of confounding or bias and a moderate probability that the relation is causal and which are directly applicable to the target population and with overall consistency of results; or • Extrapolated evidence from studies described in B
D	• Non-analytic studies, such as case reports, case series, expert opinion; or • Extrapolated evidence from studies described in C
	Good Practice Points (GPP)
☑	Recommended best practice based on the clinical experience of the guideline development group

Fig 1 | **Explanation of SIGN grades of recommendations**

- If the pain severity increases and is not controlled on a given step, move upwards to the next step of the analgesic ladder. Do not prescribe another analgesic of the same potency (GPP).
- For all patients with moderate to severe cancer pain, regardless of aetiology, start a trial of opioid analgesia. (GPP)
- Prescribe analgesia for continuous pain on a regular basis, not "as required" (D).
- Prescribe appropriate analgesia for breakthrough pain (D).

Pharmacological treatment with non-opioid drugs

Non-opioid drugs may be used at any stage of the WHO analgesic ladder. When used with opioids, their effect may be synergistic, producing better pain relief at lower doses of opioids and with potentially fewer opioid side effects.

Non-opioid analgesics

For patients at all stages of the WHO analgesic ladder, prescribe paracetamol and/or a non-steroidal anti-inflammatory drug unless contraindicated (A).

Adjuvants

Bisphosphonates—Consider bisphosphonates as part of the therapeutic regimen to treat pain in patients with metastatic bone disease (B).

Tricyclic antidepressants and anticonvulsants—For patients with neuropathic pain, prescribe either a tricyclic antidepressant (such as amitriptyline or imipramine) or an anticonvulsant (such as gabapentin, carbamazepine, or phenytoin) with careful monitoring of side effects (A).

Ketamine—Further research is needed to establish the role of ketamine as an adjuvant analgesic.

Topical analgesia—Insufficient evidence exists to support a recommendation for lidocaine 5% plaster.

Cannabinoids—Cannabinoids are not recommended for the treatment of cancer pain (A). They have been shown to be as effective as codeine in reducing nociceptive cancer pain, but adverse effects are common, dose related, and sometimes severe. Nabilone is the only cannabinoid legally available in the United Kingdom and is licensed only for use in nausea and vomiting induced by chemotherapy. No studies have assessed the effectiveness of cannabinoids on neuropathic pain due to cancer.

Pharmacological treatment with opioids

Choice of opioid

- For moderate pain (step 2 of the WHO ladder, score 3-6 out of 10 on visual analogue or numerical rating scales) prescribe weak opioids such as codeine (D).
- For severe pain (step 3 of the WHO ladder, score >6 out of 10 on visual analogue or numerical rating scales) prescribe morphine as first line oral therapy and diamorphine as first line subcutaneous therapy (D). Other options include hydromorphone, oxycodone, and transdermal fentanyl.

Breakthrough pain

Breakthrough pain is defined as a transient flare-up of pain of moderate or severe intensity arising on a background of controlled pain. Both morphine sulphate immediate release and oral transmucosal fentanyl citrate are effective at reducing breakthrough pain,

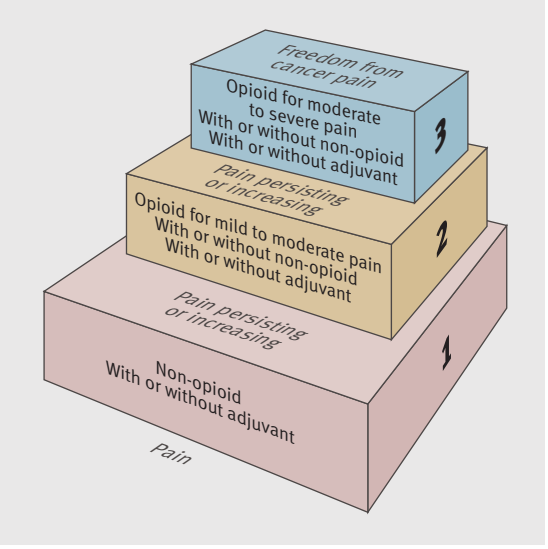

Fig 2 | **WHO analgesic "ladder" (for how to interpret it, see the section "Principles of pain management" in the main text)**

USEFUL RESOURCES FOR PATIENTS WITH CANCER PAIN

- Cancerbackup (www.cancerbackup.org.uk)—A free, one to one service that provides counselling and emotional support for people with cancer and their families and friends. It publishes over 50 booklets and a newsletter (*Cancerbackup News*) three times a year
- CancerHelp UK (www.cancerhelp.org.uk)—The patient information website of Cancer Research UK. It provides a free information service about cancer and cancer care for people with cancer and their families and includes specific information on pain control
- Marie Curie Cancer Care (www.mariecurie.org.uk)—A comprehensive cancer care charity providing practical nursing care at home and specialist multidisciplinary care through its 10 centres.

but insufficient high quality evidence exists to recommend one opioid over the other.

- Provide breakthrough analgesia for patients with moderate or severe breakthrough pain (D).
- When using oral morphine for breakthrough pain, the dose should be one sixth of the total morphine dose over 24 hours, and increased appropriately when the total dose is increased (D).
- When using oral transmucosal fentanyl citrate for breakthrough pain, establish the effective dose by upward titration independent of the total 24 hour opioid dose (GPP).

Patients with renal impairment

- Use opioids with caution and at reduced doses and/or frequency. Alfentanil, buprenorphine, and fentanyl are the safest opioids in patients with chronic kidney disease stages 4 or 5 (estimated glomerular filtration rate <30 ml/min per 1.73 m^2) (C).[11 12]
- Seek advice from a specialist in palliative care for the appropriate choice, dosage, and administration route of opioids (GPP).

Switching between strong opioids

- For patients with inadequate pain control and/or persistent intolerable side effects while taking strong opioids, provide a thorough holistic reassessment of pain and pain management (GPP).
- For patients in whom pain is not controlled and opioid side effects preclude further upward titration, switch to a different opioid (GPP).

Conversion ratios

Reported equianalgesic dose ratios (the ratio of the dose of opioids required to produce the same analgesic effect) for strong opioids vary widely in published studies, manufacturers' literature, and reference sources. The table shows conversion ratios for commonly used opioids.

- When converting from one opioid to another, regular assessment and reassessment of efficacy and side effects is essential because of the lack of evidence on equianalgesic dose ratios and interindividual variations. Titrate the dose up or down according to pain control and/or adverse effects. If in doubt, seek specialist advice (GPP).

Constipation

Prescribe laxatives for all patients taking opioids and adjust according to bowel habit (GPP).

Non-pharmacological treatment

Complementary therapies

Insufficient evidence exists to recommend any of the following: massage plus aromatherapy; music therapy; acupuncture; transcutaneous electrical nerve stimulation; reflexology; hypnotherapy; and reiki.

Radiotherapy to relieve pain from bone metastases

- Where bone metastases cause pain that is difficult to control with drugs, refer for consideration of external beam radiotherapy or radioisotope treatment (B).
- Where malignant vertebral collapse or pelvic bone metastases cause pain that is difficult to control with drugs, refer for consideration of vertebroplasty or percutaneous cementoplasty respectively (D).

Suggested dose conversion ratios*

Current opioid	New opioid and/or new route of administration	How to calculate the initial 24 hour dose† of new opioid and/or new route from the current 24 hour dose
Oral to oral route conversions		
Oral codeine	Oral morphine	Divide by 10
Oral tramadol	Oral morphine	Divide by 5
Oral morphine	Oral oxycodone	Divide by 2
Oral morphine	Oral hydromorphone	Divide by 7.5
Oral to transdermal route conversions		
Oral morphine	Transdermal fentanyl	Refer to manufacturer's information‡
Oral morphine	Transdermal buprenorphine	Seek advice from specialist in palliative care
Oral to subcutaneous route conversions		
Oral morphine	Subcutaneous morphine	Divide by 2
Oral morphine	Subcutaneous diamorphine	Divide by 3
Oral oxycodone	Subcutaneous morphine	No change
Oral oxycodone	Subcutaneous oxycodone	Divide by 2
Oral oxycodone	Subcutaneous diamorphine	Divide by 1.5
Oral hydromorphone	Subcutaneous hydromorphone	Seek advice from specialist in palliative care
Other route conversions rarely used in palliative medicine		
Subcutaneous or intramuscular morphine	Intravenous morphine	No change
Intravenous morphine	Oral morphine	Multiply by 2
Oral morphine	Intramuscular morphine	Divide by 2

*The conversion ratios—which are based on available evidence (mainly observational and often single dose studies)[4]—are conservative in the direction specified; if converting in the reverse direction, reduce the dose by a further one third after conversion, or seek specialist advice. These are initial suggested conversion ratios; take into account the patient's clinical condition and prescribe breakthrough analgesia as necessary. After opioid conversion, monitor and adjust the dose up or down according to efficacy and side effects.
†The same units must be used for both opioids or administration routes—for example, milligrams of morphine to milligrams of oxycodone.
‡The conversion ratios of oral morphine to transdermal fentanyl specified by the manufacturers vary from about 100:1 to 150:1.

Anaesthetic interventions

Despite management by multidisciplinary teams according to the WHO guidelines, up to a fifth of patients with cancer may have poorly controlled pain.[3 13] For patients with pain that is poorly controlled despite optimal systemic or oral therapy, do the following:

- Refer to an anaesthetist with expertise in pain medicine, for consideration of an appropriate intervention; patients most likely to benefit include those with locally advanced disease, neuropathic pain, or marked movement related pain (GPP).
- Consider interventions such as coeliac plexus block and neuraxial opioids to improve pain control and quality of life (B).

Overcoming barriers

Cognitive behavioural therapy is not always readily available to patients with cancer pain. Resolving the lack of availability may involve redesigning services to look at different ways of providing such therapy as well as providing access to a clinical psychologist with an interest in managing pain. Patients should be reassured about the low probability of physical addiction to opioids and encouraged to adhere to treatment regimens. Access to specialist procedures such as cementoplasty and vertebroplasty may also need to be improved.

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Commentary: Controversies in SIGN guidance on pain control in patients with cancer

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Most patients with cancer experience pain. The ambitious task of the Scottish Intercollegiate Guidelines Network (SIGN) when producing its guidelines on pain control in patients with cancer was to achieve a single set of evidence based recommendations for professionals delivering generic palliative care and for those in specialist palliative care units, across both the acute and community settings. Management of complex pain requires good assessment, good communication, attention to spirituality and psychological issues, and detailed knowledge of analgesics. As such, this comprehensive, well researched guidance from SIGN will be an important resource.[1]

The availability and delivery of different opioids for breakthrough pain has greatly increased recently, particularly for new rapid onset opioids. Misuse of opioids poses serious risks to patients, clinicians, and society as a whole. Drug exposure in itself is not sufficient to cause a substance related disorder, but a fast acting opioid such as fentanyl, with strong affinity for μ-opioid receptors and kinetics, may have a higher risk than other preparations of triggering misuse.[2] To minimise the risk we must evaluate the real risk of misuse, and use these new preparations with caution[3]; however, whether this approach is feasible when the definition of breakthrough pain is so non-specific is unclear.[2] The SIGN guidance does not mention potential misuse, addiction, dependence, and tolerance and is therefore incomplete. This area warrants further discussion, to devise a clear strategy for monitoring the adverse effects of rapid onset opioids and any aberrant behaviour of patients taking them. Such a monitoring

strategy is included in the guidelines on chronic non-cancer pain from the American Society of Interventional Pain Physicians.[4]

Although the SIGN guidance on the use of common analgesics is comprehensive, secondary and tertiary centres will require more detailed guidance for the more sophisticated pain management strategies described, such as the use of ketamine. Ketamine is infrequently used and has severe side effects such as dysphoria. The guidance recommends supervision by a specialist in pain relief or a palliative medicine specialist but does not provide more detailed advice.

Equity in provision of proved anticancer treatments is an ongoing challenge. The guideline recommends cognitive behavioural therapy as part of a comprehensive treatment strategy, citing meta-analyses that show the therapeutic role of such therapy in pain control by modifying behaviour patterns and the emotional response to actual and anticipated pain. However, timely access to professionals with adequate skills in this therapy is limited, particularly for those in the palliative phase of their illness, who require immediate and/or intensive treatment.

We lack high quality evidence in several areas, including frequency and severity of psychological distress or depression; effectiveness of morphine as first line strong opioid of choice; safety of different opioids in renal impairment; efficacy of newer drugs; and risk of osteonecrosis of the jaw secondary to bisphosphonates. The guidelines recommend trying to fill some of these gaps through routine clinical audit, to determine "proportions" of patients in 19 categories—such as patients screened for depression or renal impairment, those in pain, and those receiving specific treatments, including antidepressants, bisphosphonates, or different opioid preparations. These data would form a valuable baseline measure of clinical need and clinical practice.

A key research goal should also be to establish a large, clinical, palliative care database that includes standardised assessment tools for measuring patient reported outcomes. Although the evidence for which tool(s) to use is poor, multidimensional tools such as the brief pain inventory are validated for use in many settings and languages.[5] Such data will better inform policy for end of life care.

Debate continues about factors that might influence response to different analgesics.[6] From our growing understanding of genetic variation in predicting both analgesic response[7] and side effect profiles[8] for different opioids, translational research should enable us to target the right drug of the right dose at an individual patient, reducing both the time taken to achieve adequate symptom control and the incidence of drug related side effects.

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Competing interests: JR was a member of the NICE consideration panel for cancer care (2007), which decided on the oncology drugs for which NICE should provide guidance; the panel does not consider palliative care drugs.
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UNCERTAINTIES PAGE

Managing the anticoagulated patient with atrial fibrillation at high risk of stroke who needs coronary intervention

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Given the common association between atrial fibrillation and coronary artery disease, more patients with atrial fibrillation are presenting with acute coronary syndromes or need percutaneous coronary intervention, with or without coronary stenting. Patients with atrial fibrillation who are at high risk of stroke benefit greatly from thromboprophylaxis with oral anticoagulants.[1]

Dual antiplatelet treatment—aspirin plus a thienopyridine (clopidogrel or less often ticlopidine)—is needed after acute coronary syndrome to prevent recurrent cardiac ischaemia (recommended for 12 months[2]) or stent thrombosis (a minimum of four weeks for bare metal stents and 6-12 months for drug eluting stents after elective procedures[3]). But adding dual antiplatelet treatment to the regimen of someone

This is a series of occasional articles that highlights areas of practice where management lacks convincing supporting evidence. The series advisers are David Tovey, editorial director, BMJ Knowledge, and Charles Young, editor of BMJ Clinical Evidence, and editor in chief, BMJ Point of Care.

already receiving oral anticoagulation for stroke prevention increases the risk of life threatening bleeds. For example, when warfarin is combined with aspirin in patients with peripheral vascular disease, the absolute risk of life threatening bleeding increases from 1.2% to 4% over three years (relative risk 3.41; relative risk of intracranial bleeding 15.2).[4] Triple therapy with warfarin, clopidogrel, and aspirin may even increase the relative risk of a life threatening bleed around 10-fold in vulnerable patients with multiple comorbidities and risk factors for bleeding.

A fine balance is therefore needed between stroke prevention and increased risk of bleeding in high risk patients with atrial fibrillation, recurrent cardiac ischaemia, or stent thrombosis who are taking triple antithrombotic therapy (aspirin, clopidogrel, and oral anticoagulation).

What is the evidence of the uncertainty?

No systematic review or randomised trial has dealt with this question in people receiving anticoagulation for atrial fibrillation.

Case series of patients with atrial fibrillation undergoing percutaneous coronary intervention or stenting found that cardiologists varied greatly in the antithrombotic regimens used.[5,6] The largest published series of antithrombotic treatments in patients with atrial fibrillation (n=426) undergoing percutaneous coronary intervention and stent implantation found that lack of anticoagulation significantly increased mortality (17.8% *v* 27.8%; hazard ratio 3.43) and major adverse cardiac events (26.5% *v* 38.7%; hazard ratio 4.9), with no significant difference in major bleeding events.[6] Registry analyses of patients having percutaneous coronary intervention, which included some patients with atrial fibrillation on anticoagulation (presumed to be at high risk of stroke, but not clearly stated), reported a higher risk of bleeding with triple therapy in most[7-9] but not all studies.[10] Stroke and thromboembolism rates were inconsistently reported.

Other reports after myocardial infarction have shown an increased risk of bleeding in patients taking warfarin plus aspirin, which is exacerbated by adding a thienopyridine.[11,12] Also, higher doses of aspirin (300 *v* 75 mg) confer a greater risk of gastrointestinal bleeding. Of note, treatment with aspirin plus clopidogrel is inferior to warfarin for preventing strokes in high risk patients with atrial fibrillation (annual thromboembolic risk 5.6% with aspirin plus clopidogrel versus 3.93% with warfarin—an absolute difference of 1.67%).[13] Also, the effects of aspirin on the prevention of stroke or vascular events are not additive to those of warfarin, but adding aspirin significantly increases the number of haemorrhages.1.67%).[14]

Over a short time (for example, weeks), the absolute risk of cardiogenic embolism as a result of stopping warfarin in a patient taking antiplatelet therapy for stent prophylaxis is probably small, and some clinicians may think this an acceptable price to pay for avoiding life threatening bleeding from triple combination therapy.

Suggested management strategy for patients with non-valvular atrial fibrillation requiring anticoagulation and percutaneous coronary intervention with stenting. Adapted, with permission, from Lip and Karpha[5]

Stroke risk category	"Usual" strategy recommended	Perceived potential bleeding risk	Acute coronary syndrome at presentation	Management after percutaneous coronary intervention*	
				If patient has bare metal stent	If patient has drug eluting stent
Low	Aspirin	Not relevant	Not relevant	Aspirin plus clopidogrel for 4 weeks, then aspirin	Aspirin plus clopidogrel for 6-12 months, then aspirin
High	Warfarin	Low	No	Use bare metal stent if possible; triple therapy with warfarin, aspirin, and clopidogrel for 2-4 weeks; then warfarin and clopidogrel for up to month 12; then warfarin alone	Triple therapy with warfarin, aspirin, and clopidogrel for 3-6 (or more) months; then warfarin and clopidogrel for up to month 12; then warfarin alone
			Yes	Triple therapy with warfarin, aspirin, and clopidogrel for 3-6 (or more) months; then warfarin and clopidogrel for up to month 12, then warfarin alone	Triple therapy with warfarin, aspirin, and clopidogrel for 3-6 (or more) months; then warfarin and clopidogrel for up to month 12; then warfarin alone
High	Warfarin	High†	No	Use bare metal stent if possible; triple therapy with warfarin, aspirin, and clopidogrel for 4 weeks; then warfarin alone	Triple therapy with warfarin, aspirin and clopidogrel for 4 weeks, then warfarin and clopidogrel for up to month 12; then warfarin alone
			Yes	Triple therapy with warfarin, aspirin, and clopidogrel for 4 weeks; then warfarin and clopidogrel for up to month 12; then warfarin alone	Triple therapy with warfarin, aspirin, and clopidogrel for 4 weeks; then warfarin and clopidogrel for up to month 12; then warfarin alone

These recommendations are based on extrapolation from diverse studies in different populations, given the lack of evidence on the optimal management for such patients. Also, although coronary stents are usually used these days, optimal balloon-only angioplasty with bail-out stenting may be used in highly selected patients or lesions. These recommendations are for post-percutaneous coronary intervention (or stenting). If surgery is needed, triple (or dual) antithrombotic therapy is associated with excess bleeding, and many surgeons request that antiplatelet therapy be stopped before surgery.

*Aspirin 75 mg/day; clopidogrel 75 mg/day. Warfarin dose adjusted to target international normalised ratio 2.0-2.5.

†Pay particular attention to the following risk factors: age over 75, taking antiplatelet drugs or non-steroidal anti-inflammatory drugs, taking multiple other drugs (polypharmacy); uncontrolled hypertension; a history of bleeding (for example, peptic ulcer or cerebral haemorrhage) or poorly controlled anticoagulation therapy.

Some clinicians also think it best to avoid warfarin altogether while antiplatelet treatment is needed (for example, for up to 12 months after percutaneous coronary intervention). But without warfarin, up to 6-8% of patients with atrial fibrillation at very high risk of stroke who are taking antiplatelet treatment will have a stroke each year,[15] and stroke in such patients is associated with higher mortality, greater disability, and higher risk of recurrence compared with those without atrial fibrillation.

Is ongoing research likely to provide relevant evidence?

Given the nature of the study population and the concerns of interventional cardiologists over stent thrombosis, randomised placebo controlled trials are unlikely to be performed. Much of the evidence for now would have to be informed by non-randomised registry analyses or cohort studies. Future randomised trials using new antithrombotic agents (with a better safety profile than warfarin) may ultimately provide some evidence.

What should we do in the light of the uncertainty?

Because dual antiplatelet drugs need to be used for longer with drug eluting stents, interventional cardiologists should avoid using such stents in patients with atrial fibrillation, who require long term anticoagulation.

Recent guidelines state that after percutaneous coronary intervention in patients with atrial fibrillation, low dose aspirin (<100 mg/day) or clopidogrel (75 mg/day), or both, may be given concurrently with anticoagulation to prevent myocardial ischaemic events.[2 16] The maintenance regimen should be clopidogrel 75 mg daily plus warfarin (target INR 2-3). Clopidogrel is recommended for at least one to six months after stent implantation (depending on type of stent), and at least 12 months in selected patients, after which warfarin may be continued as monotherapy in the absence of a subsequent coronary event.[16] The UK National Institute for Health and Clinical Excellence (NICE, www.nice.org.uk) guidelines on the management of atrial fibrillation do not specifically deal with this problem, but they state that it is "a matter for clinical judgment on the appropriateness, duration and safety of the concomitant administration" of warfarin and antiplatelet drugs.[17]

However, the two guidelines do not consider the presentation with acute coronary syndrome or the perceived bleeding risk.[16 17] Clinicians may offer a pragmatic approach that considers these factors (table).[5] This approach is broadly similar to an international expert consensus guideline on antithrombotic treatment in patients treated with oral anticoagulation undergoing coronary artery stenting, which also includes a systematic review of the literature.[18]

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