GUIDELINES

The management of atrial fibrillation: summary of updated 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.

Atrial fibrillation is increasingly common,[1] with more than 800 000 people being affected in England.[2] Many people are managed in primary care without hospital involvement. The condition is a major cause of morbidity, particularly stroke, and it reduces life expectancy. Strokes caused by atrial fibrillation are largely avoidable—most can be prevented by anticoagulation. Yet uptake of anticoagulation by people with known atrial fibrillation who are at increased risk of stroke is suboptimal.[3-5]

Since the publication of the 2006 guidance, several developments relating to risk stratification, stroke prevention, and rhythm management have led to a partial update on the 2006 guidance. This article summarises the most recent recommendations from the National Institute for Health and Care Excellence (NICE).[6]

Recommendations

NICE recommendations are based on systematic reviews of 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. All recommendations below should be in accordance with the NICE patient experience guideline,[7] and the benefits and risks of treatment should be discussed with the patient.

Diagnosis and assessment

- Perform manual pulse palpation to assess for the presence of an irregular pulse, which might be indicative of underlying atrial fibrillation in people presenting with any of the following: breathlessness or dyspnoea, palpitations, syncope or dizziness, chest discomfort, stroke or transient ischaemic attack. (Recommendation from 2006 guideline.)
- Perform electrocardiography (ECG) in all people, whether symptomatic or not, in whom atrial fibrillation is suspected because an irregular pulse has been detected. (Recommendation from 2006 guideline.)
- In people with suspected paroxysmal atrial fibrillation undetected by standard ECG:
  - Use 24 hour ambulatory ECG in those with suspected asymptomatic episodes or symptomatic episodes less than 24 hours apart
  - Use event recorder ECG in those with symptomatic episodes more than 24 hours apart. (Recommendation from 2006 guideline.)

Components of a care package for people with atrial fibrillation

- Stroke awareness and measures to prevent stroke*
- Rate control
- Assessment of symptoms for rhythm control
- Who to contact for advice if needed
- Psychological support if needed
- Up to date and comprehensive education and information on:
  - Cause, effects, and possible complications of atrial fibrillation
  - Management of rate and rhythm control
  - Anticoagulation
  - Practical advice on anticoagulation[8]
  - Support networks (such as cardiovascular charities)

*Examples of stroke awareness include information on the symptoms of stroke and how atrial fibrillation can lead to a stroke; measures to prevent stroke include anticoagulation for atrial fibrillation.

Table 1 | CHA_2DS_2-VASc stroke risk stratification. Adapted, with permission, from Lip and colleagues[9]

Risk factor	Score
Congestive heart failure or left ventricular dysfunction	1
Hypertension	1
Age ≥75 years	2
Diabetes mellitus	1
Stroke or transient ischaemic attack or systemic thromboembolism	2
Vascular disease*	1
Age 65-74 years	1
Female sex (sex category)	1

*Vascular disease defined as previous myocardial infarction, peripheral arterial disease, or aortic plaque.

Personalised package of care

- Offer people with atrial fibrillation a personalised package of care (box). Ensure that the package of care is documented and delivered. (New recommendation.)

Referral

- Refer people promptly at any stage if treatment does not control the symptoms of atrial fibrillation and more specialised management is needed. Prompt referral was defined as no longer than four weeks after the final failed treatment or no longer than four weeks if atrial fibrillation recurs after cardioversion and further specialised management is needed. (New recommendation.)

Assessment of stroke and bleeding risks

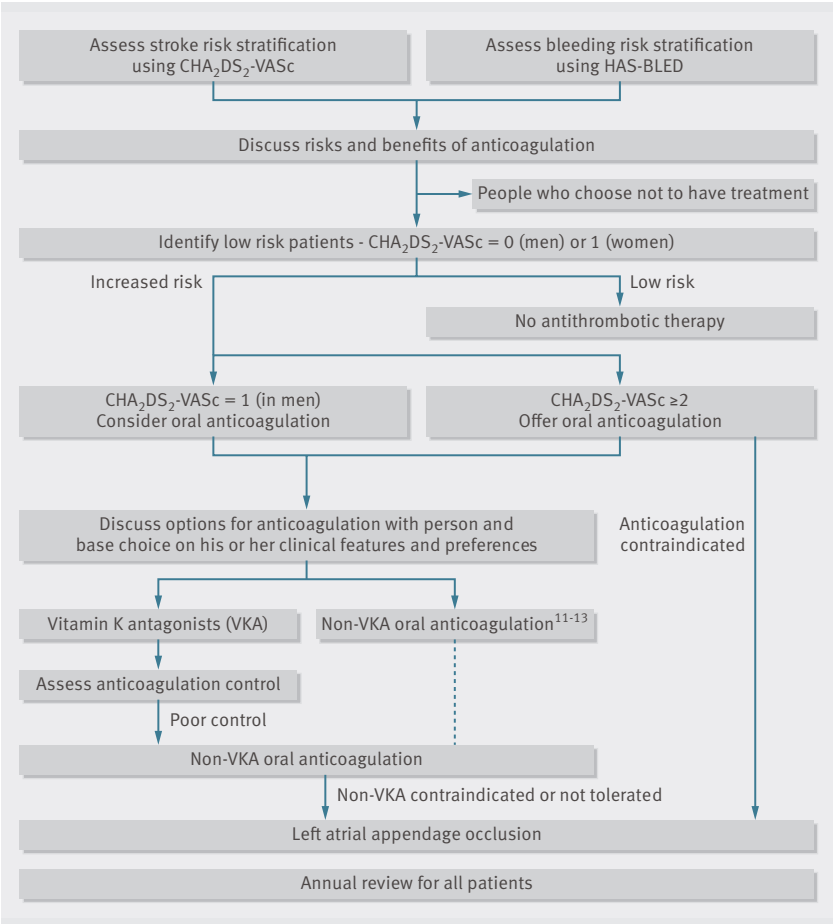
Stroke and bleeding risk should be assessed in all people with atrial fibrillation.

- Use the CHA_2DS_2-VASc (table 1)[9] score to assess stroke risk in people with any of the following:

Table 2 | HAS-BLED bleeding risk score. Adapted, with permission, from Pisters and colleagues[10]

Risk factor	Score
Hypertension	1
Abnormal renal and liver function (1 point each)	1 or 2
Stroke	1
Bleeding	1
Labile international normalised ratios	1
Elderly (age >65 years)	1
Drugs or alcohol (1 point each)	1 or 2
Maximum score	9

  - Symptomatic or asymptomatic paroxysmal, persistent, or permanent atrial fibrillation
  - Atrial flutter
  - A continuing risk of the recurrence of arrhythmia after cardioversion back to sinus rhythm. (New recommendation.)
- Use the HAS-BLED (table 2)[10] score to assess the risk of bleeding in people who are starting, or have started, anticoagulation and to highlight, correct, and monitor modifiable risk factors:
  - Uncontrolled hypertension
  - Poor control of international normalised ratio (INR; "labile INRs")
  - Concurrent drugs, such as concomitant use of aspirin or a non-steroidal anti-inflammatory drug
  - Harmful alcohol consumption. (New recommendation.)
- When discussing the benefits and risks of anticoagulation:
  - For most people the benefit of anticoagulation outweighs the risk of bleeding
  - For people with an increased risk of bleeding the benefit of anticoagulation may not always outweigh the bleeding risk, and careful monitoring of bleeding risk is important. (New recommendation.)
- Do not withhold anticoagulation solely because the person is at risk of having a fall. (New recommendation.)



Stroke prevention in people with non-valvular atrial fibrillation

Drug treatments to prevent stroke (figure)

The guideline revision emphasises that people at very low risk, who should not receive an anticoagulant, should be identified first, with anticoagulation considered or offered to the remainder, taking bleeding risk into account. Anticoagulation may be with a non-vitamin K antagonist oral anticoagulant (apixaban, dabigatran etexilate, or rivaroxaban, in accordance with individual NICE appraisals[11-13]) or a vitamin K antagonist (such as warfarin).

- Do not offer stroke prevention treatment to people aged under 65 years with atrial fibrillation and no risk factors other than their sex (that is, very low risk of stroke equating to CHA_2DS_2-VASc score of 0 for men or 1 for women). (New recommendation.)
- Consider anticoagulation for men with a CHA_2DS_2-VASc score of 1. Take the bleeding risk into account. (New recommendation.)
- Offer anticoagulation to people with a CHA_2DS_2-VASc score of 2 or above, taking bleeding risk into account. (New recommendation.)
- Discuss options for anticoagulation with the person and base choice on his or her clinical features and preferences. (New recommendation.)
- Do not offer aspirin monotherapy solely for stroke prevention to people with atrial fibrillation. (New recommendation.)

Assessing anticoagulation control with vitamin K antagonists

For people receiving a vitamin K antagonist, adequacy of anticoagulant control should be assessed.

- Calculate individual time in therapeutic range (TTR) at each visit. When calculating TTR:
  - Use a validated method of measurement, such as the Rosendaal method,[14] for computer assisted dosing or proportion of tests in range for manual dosing
  - Exclude measurements taken during the first six weeks of treatment
  - Calculate TTR over a maintenance period of at least six months. (New recommendation.) [Note: TTR is a means of assessing the quality of anticoagulant control—that is, the proportion of time an individual patient's INR values are within the target range. It is expressed as a percentage and assumes a linear change between INR results. A higher TTR is associated with a reduction in both bleeding and thrombotic events.]

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- Intravenous fluid therapy for adults in hospital: summary of NICE guidance (*BMJ* 2013;347:f7073)
- Secondary prevention for patients after a myocardial infarction: summary of updated NICE guidance (*BMJ* 2013;347:f6544)

- Reassess anticoagulation for a person with poor anticoagulation control shown by any of the following:
  - Two INR values higher than 5 or one INR value higher than 8 within the past six months
  - Two INR values less than 1.5 within the past 6 months
  - TTR less than 65%. (New recommendation.)
- When reassessing anticoagulation, take into account and, if possible, correct the following factors that may contribute to poor anticoagulation control:
  - Cognitive function
  - Adherence to prescribed treatment
  - Illness
  - Interacting drugs
  - Lifestyle factors including diet and alcohol consumption. (New recommendation.)
- If poor anticoagulation control cannot be improved, evaluate risks and benefits of alternative stroke prevention. (New recommendation.) [Note: The GDG agreed that a logical alternative would be to offer one of the non-vitamin K antagonist oral anticoagulants.]

Review of stroke and anticoagulant risk

All people with atrial fibrillation should undergo review at least annually.

- For people not taking an anticoagulant, review stroke risk when they reach age 65 or if they develop any of the following at any age:
  - Diabetes
  - Heart failure
  - Peripheral arterial disease
  - Coronary heart disease
  - Stroke, transient ischaemic attack, or systemic thromboembolism. (New recommendation.)
- For people who are not taking an anticoagulant, review stroke and bleeding risks annually. Ensure that all reviews and decisions are documented. (New recommendation.)
- For people who are taking an anticoagulant, review the need for anticoagulation and the quality of anticoagulation at least annually, or more often if clinically relevant events that affect anticoagulation or bleeding risk occur. (New recommendation.)

Left atrial appendage occlusion for people unable to take anticoagulants

This is a catheter based technique for closure or obliteration of the left atrial appendage, which is thought to be the major source of thrombus that causes stroke and peripheral thromboembolism in people with atrial fibrillation.

- Consider left atrial appendage occlusion if anticoagulation is contraindicated or not tolerated. (New recommendation.)

Rate and rhythm control

There is currently no evidence that rhythm management is superior to rate control in preventing stroke or reducing mortality. The main treatment objective is therefore control of symptoms.

- Offer rate control as the first line strategy to people with atrial fibrillation except for those in whom a rhythm control strategy would be more suitable on the basis of clinical judgment (these include people with new onset atrial fibrillation or atrial fibrillation with a reversible cause). (New recommendation.)
- Offer a standard β blocker (a β blocker other than sotalol) or a rate limiting calcium channel blocker as initial monotherapy to people with atrial fibrillation who need drug treatment as part of a rate control strategy. (New recommendation.)
- Consider digoxin monotherapy for people with non-paroxysmal atrial fibrillation only if they are sedentary (do no physical exercise or very little). (New recommendation.)
- If monotherapy does not control symptoms, and if continuing symptoms are thought to be caused by poor ventricular rate control, consider combination therapy with any two of the following:
  - A β blocker
  - Dilitazem
  - Digoxin. (New recommendation.)
- Consider pharmacological or electrical rhythm control (or both) for people with atrial fibrillation whose symptoms continue after their heart rate has been controlled or for whom a rate control strategy has not been successful. (New recommendation.)
- Assess the need for drug treatment for long term rhythm control. (New recommendation.) [Note: Drug treatment for long term rhythm control might be needed in people with paroxysmal atrial fibrillation to maximise their time in sinus rhythm, or after cardioversion in people who are thought likely to relapse, to increase the likelihood of maintaining sinus rhythm.]
- If drug treatment for long term rhythm control is needed, consider a standard β blocker (a β blocker other than sotalol) as first line treatment unless there are contraindications. (New recommendation.) [Note: Examples of possible contraindications include excessive bradycardia, asthma, or peripheral vascular disease.]
- If β blockers are contraindicated or unsuccessful, assess the suitability of alternative drugs for rhythm control, taking comorbidities into account. (New recommendation.)

Non-pharmacological management of rate and rhythm

Left atrial ablation is an effective option when drug management has failed. Ablation treatment has a better outcome when undertaken earlier rather than later and for paroxysmal rather than persistent atrial fibrillation. Pacing followed by atrioventricular node ablation is an alternative to left atrial ablation. Pacing followed by atrioventricular node ablation does not restore sinus rhythm but successfully limits ventricular rate.

- If drug treatment has failed to control symptoms of atrial fibrillation or is unsuitable:
  - Offer left atrial catheter ablation to people with paroxysmal atrial fibrillation
  - Consider left atrial catheter or surgical ablation for people with persistent atrial fibrillation (New recommendation)

- Consider left atrial surgical ablation at the same time as other cardiothoracic surgery for people with symptomatic atrial fibrillation. (New recommendation)
- Consider pacing and atrioventricular node ablation for people with permanent atrial fibrillation and symptoms of left ventricular dysfunction thought to be caused by high ventricular rates. (New recommendation)
- When considering pacing and atrioventricular node ablation, reassess symptoms and the consequent need for ablation after pacing has been carried out and drug treatment further optimised. (New recommendation)

Overcoming barriers

Anticoagulation is underused in the management of atrial fibrillation.[4 5] In older people in particular, aspirin is often used in preference to anticoagulation,[3] even though anticoagulation has been shown to reduce stroke rates by about 50% in this population, compared with aspirin.[15] We believe the new guideline deals with these problems through paradigm change, identifying low risk people in whom anticoagulation is not indicated, and making it clear that aspirin is no longer considered a cost effective alternative.

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EASILY MISSED?

Copper deficiency

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KEY POINTS

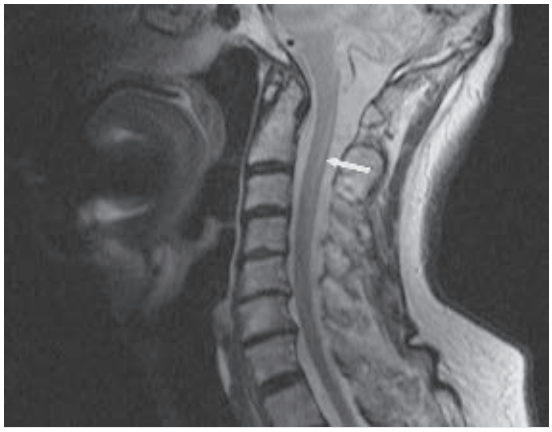
Copper deficiency is an under recognised cause of cytopenias and myeloneuropathy

Copper deficiency may masquerade as a myelodysplastic syndrome or vitamin B_{12} deficiency; it might also co-exist with B_{12} deficiency

The neurological sequelae of copper deficiency can be debilitating and irreversible, making prompt recognition and treatment essential for successful outcomes

Clinicians should have a low threshold for measuring serum copper in patients with unexplained and refractory cytopenias or myeloneuropathy, especially in the context of previous upper gastrointestinal tract surgical procedures, excess zinc exposure, or malabsorption

A 73 year old man with treated pernicious anaemia and partial gastrectomy 30 years earlier consulted his GP with a 12 month history of progressive numbness of his feet and hands. A haematology opinion for normocytic anaemia, neutropenia, and lymphopenia led to an unremarkable bone marrow biopsy. Increasing unsteadiness and falls prompted neurology referral. He was found to have sensory ataxia with clinical, radiological (figure), and neurophysiological evidence of myelopathy and peripheral neuropathy. Vitamin B_{12} level was high, consistent with ongoing replacement. Low serum copper confirmed hypocupraemic myeloneuropathy. Copper replacement achieved resolution of the cytopenia within four weeks, and slow but minimal neurological improvement was seen over more than nine months of follow-up.



T2 weighted sagittal magnetic resonance image of cervical spine showing increased signal intensity (arrowed) involving dorsal columns of the cervical spinal cord

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- Bladder cancer in women (*BMJ* 2014;348:g2171)
- Subdural haematoma in the elderly (*BMJ* 2014;348:g1682)
- Intestinal malrotation and volvulus in infants and children (*BMJ* 2013;347:f6949)
- Lisfranc injuries (*BMJ* 2013;347:f4561)
- Spontaneous oesophageal rupture (*BMJ* 2013;346:f3095)

What is hypocupraemia?

Copper is an essential trace element that plays a crucial role in the normal functioning of the neurological, haematological, vascular, skeletal, and antioxidant systems.[1 2] Copper is absorbed in the stomach and proximal duodenum, but absorption can be impaired after upper gastrointestinal surgery. Such surgery, although not the sole cause of copper deficiency (hypocupraemia), is increasingly recognised as an important risk factor.[3] Copper deficiency leads to several clinical presentations including cytopenia and profound neurological deficits.[1-4]

How common is copper deficiency?

Evidence is limited but several reports describe symptomatic copper deficiency.[1-5] In a case series of 136 patients with gastric bypass surgery, 9.6% had hypocupraemia.[6] Two other case series of 64 and 141 bariatric surgery patients respectively reported substantial hypocupraemia in 23% at 6 months and 70% at 3 years,[7] and a progressive reduction in average serum copper concentrations over five years.[8]

Reliable data on the overall population at risk of hypocupraemia from all causes, including bariatric surgery, are not available, but longitudinal collection of data would be valuable.

Why is copper deficiency missed?

Copper deficiency is an under recognised cause of neurological dysfunction and a spectrum of cytopenias.[1] A retrospective review of 40 patients with hypocupraemia found the median interval from initial presentation with neurological or haematological findings to diagnosis of copper deficiency to be 1.1 years (range 10 weeks to 23 years).[2] Misdiagnosis as a myelodysplastic syndrome might occur, given the similar haematolopathological findings including anaemia, leucopenia, and less commonly, thrombocytopenia.[1 2] This is suggested by a recent retrospective analysis of copper deficiency in Scotland, which found that four out of 16 cases eventually diagnosed with hypocupraemia were initially seen by a haematologist.[1]

The clinical presentation is often clinically and radiologically indistinguishable from subacute combined degeneration (SACD) seen in patients with vitamin B_{12} deficiency. Confirmation of B_{12} deficiency in a patient with a clinical presentation resembling SACD might understandably lead to testing for copper deficiency not being undertaken, even though hypocupraemia might be comorbid with B_{12} deficiency, particularly in patients who have undergone gastric surgery.[4 9]

Moreover, the interval between gastric surgery and the onset of clinical symptoms can be long.[4 5 9] A retrospective review of 55 cases of hypocupraemia found that the interval between upper gastrointestinal surgery and symptom onset ranged from five to 26 years in the bariatric group and 10 to 46 years in the non-bariatric group.[4] Such long intervals might lead to diagnostic delay because a causal association might not be so readily considered, but observations of gradually declining copper levels over years lend clear support to causation.[8]

Why does it matter?

Although copper deficiency is rare, its early identification is essential to minimise its neurological sequelae, which are severely disabling and often irreversible.[1-4] Copper deficiency can be easily treated and copper supplementation largely prevents further neurological decline, but neurological improvement is variable.[1-4] A retrospective cohort study in Scotland, which identified 16 patients manifesting clinical sequelae of hypocupraemia (12 with neurological features), found that only 25% of patients show some improvement while 33% might continue to deteriorate with treatment.[1] The haematological effects are relatively easily reversible, with 93% of cytopenias responding to copper replacement and management of the underlying cause.[1]

How is copper deficiency diagnosed?

Clinical features

The diagnosis should be considered in anyone with characteristic neurological or haematological abnormalities (or both), particularly patients with risk factors (box 1). Copper and zinc are competitively absorbed from the gastrointestinal tract; hence zinc excess leads to copper deficiency.[1 4]

Neurological manifestations include myelopathy, myeloneuropathy, and peripheral neuropathy.[1 4] Patients characteristically present with lower limb paraesthesias and gait disorder with sensory ataxia or spasticity or both.

Investigations

Initial investigations in primary care should include a full blood count and measurement of serum copper. Typical haematological abnormalities are anaemia and leucopenia. Anaemia which might be microcytic, macrocytic, or normocytic, is the commonest cytopenia, followed by leucopenia; thrombocytopenia is infrequent.[1 2] Laboratory indicators of copper deficiency include low serum copper.[1 2 4] Vitamin B_{12} level should also be tested as B_{12} deficiency is an important differential diagnosis and may sometimes co-exist with copper deficiency. Zinc levels should also be requested if zinc excess is suspected. American bariatric surgery clinical practice guidelines recommend testing for copper deficiency in post-bariatric surgery patients with anaemia,

This is one of a series of occasional articles highlighting conditions that may be more common than many doctors realise or may be missed at first presentation. The series advisers are Anthony Harnden, university lecturer in general practice, Department of Primary Health Care, University of Oxford, and Richard Lehman, general practitioner, Banbury. To suggest a topic, please email us at practice@bmj.com

Risk factors for copper deficiency[4]

- Upper gastrointestinal tract surgery
- Gastrectomy
- Bariatric surgery
- Small bowel resection or bypass
- Zinc overload
- Zinc supplementation
- Ingestion of zinc containing dental fixatives
- Malabsorption syndromes

neutropenia, myeloneuropathy, and impaired wound healing.[10] Specialist referral would generally be pursued for suspected symptomatic hypocupraemia.

Specialist neurological investigations typically include magnetic resonance imaging and neurophysiology. Spinal cord magnetic resonance imaging is abnormal in about 47% of patients with copper deficiency myelopathy and might show increased T2 signal, most commonly in the dorsal midline cervical and thoracic cord.[4] Neurophysiological studies might show axonal sensorimotor polyneuropathy.[4]

How is copper deficiency managed?

Treatment includes management of the underlying cause and copper supplementation. No studies have investigated with the dose, route, duration, or formulation of copper for supplementation. The salts that are commonly used include copper gluconate, copper sulphate, and copper chloride.[4] Copper can be given orally or intravenously. The American Society for Metabolic and Bariatric Surgery Clinical Practice guidelines recommend routine oral copper supplementation (2 mg/d).[10] These guidelines advise intravenous copper (2-4 mg/d) for six days for severe deficiency and subsequent treatment, or treatment of mild to moderate deficiency, with oral copper (3-8 mg/d) until levels normalise.[10] The haematological abnormalities reverse within four to 12 weeks of therapy.[1] Periodic assessment of serum copper is essential to determine adequacy of replacement; however, there are no guidelines to recommend the frequency of monitoring. In patients in whom excess zinc ingestion is the likely cause, discontinuing zinc supplementation might suffice.

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ANSWERS TO ENDGAMES, p 40

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ANATOMY QUIZ

Anatomy of the facial skeleton

A: Right zygomaticofrontal suture
B: Right orbital floor
C: Right zygomatic arch
D: Left frontal sinus
E: Left maxillary sinus
F: Left lateral maxillary wall

STATISTICAL QUESTION

Unit of observation versus unit of analysis

Statement *b* is true, whereas statements *a* and *c* are false.

PICTURE QUIZ

An unusual case of epigastric pain

1 The figures show non-occlusive acute venous thrombosis in the portal and mesenteric veins.
2 The diagnosis is acute portal vein thrombosis with superior mesenteric vein thrombosis. This condition should be considered in any patient with unexplained abdominal pain of more than 24 hours' duration.
3 Investigations should focus on determining when the thrombosis developed and on finding any underlying conditions that may have triggered it. Look for any localised predisposing factors such as cirrhosis, cancer, or acute inflammation.
4 Treatment with anticoagulants aims to stop extension of the thrombus, thereby preventing intestinal infarction and portal hypertension. Patients with cirrhosis should be screened for varices before anticoagulation is started.
5 Complications include life threatening variceal bleeds from portal hypertension and death from mesenteric infarction. In developing countries, it has been reported that 40% of portal hypertension may be caused by portal vein thrombosis.