

## NEWSLETTER

Supporting the Derbyshire Health Community

Volume 7: Issue 2

May 2008

<b>Further in this issue</b>	<b>Page 2</b>	<b>Antimicrobial treatment guidelines</b> Can patients who develop angioedema with an ACEI try an AIIRA? <b>Calcium supplements and the risk of MI</b>
	<b>Page 3</b>	<b>Management of osteoarthritis</b>
	<b>Page 5</b>	<b>Cold sore machine on NHS prescription</b> <b>Drug safety update</b> <b>Prescribing gluten-free foods</b>
	<b>Page 6</b>	<b>Tension-type headache</b>
	<b>Page 8</b>	<b>Glycaemic targets in type 2 diabetes</b>

### JAPC Update

The Joint Area Prescribing Committee (JAPC) is a countywide group covering Derbyshire County PCT and Derby City PCT. It provides recommendations on drugs and medicines management issues.

RED drugs are those where prescribing responsibility would normally lie with a hospital consultant or a specialist. AMBER drugs are those that although usually initiated within a hospital setting, could appropriately become the responsibility of the GP, under a shared care agreement. GREEN drugs are regarded as suitable for primary care prescribing. BROWN drugs are those that JAPC does not recommend for use, except in exceptional circumstances, due to lack of data on safety, effectiveness, and/or cost-effectiveness.

The most recent updates are in the table below:

<b>Drug</b>	<b>Date considered</b>	<b>Decision</b>
Virulite CS cold sore machine	April 2008	BROWN
Eucreas (vildagliptin + metformin)	April 2008	BROWN
Vildagliptin	April 2008	BROWN
Suboxone (buprenorphine + naloxone)	April 2008	BROWN
Ionsys (fentanyl transdermal system)	April 2008	RED
Mircera	April 2008	RED
Colesevalem	February 2008	BROWN
Hyaluronic acid injection	February 2008	RED

### Guidelines update

The following guidelines and shared care agreements have recently been ratified by JAPC:

- Emollient prescribing guide for adults (new)
- Antimicrobial treatment guidelines (updated)
- Neuropathic pain management in primary care (new)
- Antidepressants in moderate and severe unipolar depression (updated)
- Prevention of infection in patients with absent spleens (updated)
- Guideline on hearing loss, speech and language delay in children for use with Chesterfield Royal Hospital FT (new)
- Shared care of buprenorphine, lofexidine, methadone and naltrexone for opioid dependency (updated)
- Buccal midazolam shared care (updated)
- Sevelamer shared care for use with Derby Hospitals FT (new)
- Rivastigmine in Parkinson's disease dementia shared care for use with Derby Hospitals FT (new)

You can obtain copies of these from your Medicines Management team or from me.

## **Antimicrobial treatment guidelines**

These have been updated and approved by JAPC for the use in primary care across all of Derbyshire. Copies will be distributed in the near future.

There are two key changes:

- Doxycycline is now the first-line antibiotic for acute exacerbation of COPD (with increased and purulent sputum) and amoxicillin has been relegated to second-line. This is to try and reduce the use of amoxicillin because of its link with MRSA infection.
- There are **no** indications in the guideline for the primary care use of ciprofloxacin.

## **Can patients who develop angioedema with an ACEI try an AIIRA?**

Angioedema is a recognised adverse effect of ACE inhibitors and is thought to be due to accumulation of bradykinins. When angiotensin II receptor antagonists (AIIRAs) were first introduced it was hoped that they would not be associated with angioedema as they have a different mode of action from ACE inhibitors. However it is now known that this is not the case.

Angioedema has been reported with a number of AIIRAs and appears to be a class effect. Although the true incidence of angioedema associated with AIIRAs is not known, it is lower than that associated with ACE inhibitors. The reported incidence of ACE inhibitor induced angioedema varies between less than 0.1% and 1%, with most studies reporting an incidence of between 0.1% and 0.2%.<sup>1</sup>

There is evidence that angioedema associated with AIIRAs may be more likely to occur in patients who have experienced angioedema while taking ACE inhibitors. Two reviews of patients who developed angioedema while taking an AIIRA (involving 32 patients) found that nine had previously experienced angioedema with an ACE inhibitor.<sup>1,2</sup>

As angioedema is potentially life threatening, AIIRAs should be used with extreme caution in patients who have previously experienced angioedema while receiving ACE inhibitors. AIIRA therapy should be contemplated in these patients only if there is no other alternative.<sup>1</sup>

1. Drug Safety 2002; 25: 73-76
2. Ann Pharmacother 2000; 34: 526-528

## **Calcium supplements and the risk of MI**

According to a recent RCT in 1471 postmenopausal women (mean age 74), calcium supplementation is associated with upward trends in cardiovascular event rates<sup>1</sup>. Here is the NPCi blog review of this study<sup>2</sup>.

***What is the background to this?*** – Postmenopausal women have a high incidence of vascular disease and it has been suggested that calcium supplements might be beneficial for vascular health, as well as bone health, in these women. This New Zealand study aimed to determine the effect of calcium supplementation on myocardial infarction (MI), stroke and sudden death in healthy postmenopausal women.

***What does this study claim?*** – MI was more commonly reported in women receiving 1g/day of calcium, compared with placebo (45 events in 31 women vs. 19 events in 14 women; relative risk [RR] 2.24 [95%CI 1.20 to 4.17]; P=0.01). The composite endpoint of MI, stroke or sudden death also occurred significantly more often in the women taking calcium supplementation (101 events in 69 women vs. 54 events in 42 women; RR 1.66 [95% CI 1.15 to 2.40]; P=0.008). There was no significant difference between the groups for the other outcomes that were assessed.

*When the reported results were re-assessed following confirmation of CV events by a cardiologist (MI and sudden death) or neurologist (stroke and transient ischaemic attack [TIA]) who was blinded to the participants' treatment group, a statistically significant increase in MI remained in the calcium group (24 events in 21 women vs. 10 events in 10 women; RR 2.12 [95% CI 1.01 to 4.47]; P=0.047). However, there was no significant increase in the composite endpoint.*

*When unreported events from the national database of hospital admissions in New Zealand were added to the reported events there were no longer statistically significant differences between the groups for any of the endpoints.*

**How does this relate to other studies?** – Calcium supplementation has been shown to produce changes in cholesterol levels that might be expected to reduce cardiovascular (CV) risk. Similarly, results from observational data have suggested that a high calcium intake might protect against vascular disease. However, contrary to the authors' expectations, this study found that healthy postmenopausal women who were randomised to calcium supplementation had a higher risk of MI not a lower one. Although calcium appears to have beneficial effects on cholesterol, this does not seem to translate into a reduced CV risk, particularly the risk of MI.

The study has some limitations – in particular it was not designed to look at cardiovascular outcomes and the number of events seen was relatively small. Definite conclusions cannot be drawn, as the authors conclude, “this potentially detrimental effect should be balanced against the likely benefits of calcium on bone, particularly in elderly women”. An editorial makes similar comments.

In addition, monotherapy with calcium, as used in this study, has not been shown to reduce fractures in postmenopausal women, so it is not generally recommended. Combined calcium and vitamin D may reduce vertebral and non-vertebral fractures, but the results from controlled studies are inconclusive. The Clinical Knowledge Summaries guideline on osteoporosis recommends that calcium and vitamin D supplements should be prescribed for all women who are receiving treatment for osteoporosis (e.g. bisphosphonates) unless dietary intake is thought to be adequate. It is unclear whether calcium plus vitamin D could carry the same potential risk of MI.

**So what?** - Postmenopausal women already have an increased risk of CV disease. Those who are at particularly high risk for falls and osteoporotic fracture (e.g. the elderly) may also be at particularly high risk for CV disease. It is worrying that any benefit of calcium supplementation on bone health could potentially be cancelled out by an increase in the risk of MI. In this study the number of women needed to treat for five years to cause one MI was 44. By comparison the number needed to treat to prevent one symptomatic fracture was 50.

**Action** – Calcium supplementation alone should not generally be prescribed to postmenopausal women for fracture prevention. Clinicians should weigh up the pros and cons of calcium and vitamin D supplementation on an individual basis, taking into account the patient's risk of CV disease and osteoporosis.

There have been letters published that are critical of this trial and its conclusions<sup>3</sup>. Some point out that important confounders were not accounted for. One concludes that the excess of events was either a chance occurrence or at least not generalisable to other populations. The author's reply concludes “We have presented important, unexpected findings from the secondary analysis of a carefully conducted, randomised controlled trial. They do not definitely establish that calcium supplementation increases vascular events, but they mandate that this possibility is further investigated as a matter of urgency.”

The Medicine Management teams have reached the conclusion, based on the evidence, that in nursing and residential home residents and others at high risk of osteoporosis, falls, and fractures, the benefits of calcium + vitamin D outweighs any risk.

**Bottom line: this study should not influence the use of calcium + vitamin D preparations.**

1. BMJ Online First doi:10.1136/bmj.39440.525752.BE (published 15/8/108)
2. [www.npci.org.uk/blog/?p=57](http://www.npci.org.uk/blog/?p=57)
3. Lancet 2008; 336: 403-4

### **Management of osteoarthritis**

NICE has published its guideline on management of osteoarthritis - '[Osteoarthritis: the care and management of osteoarthritis in adults](#)' (NICE CG 59) These are some of the key priorities for implementation:

- Exercise should be a core treatment for people with osteoarthritis, irrespective of age, co-morbidity, pain severity or disability. Exercise should include local muscle strengthening and general aerobic fitness.
- Referral for arthroscopic lavage and debridement should **not** be offered as part of treatment for osteoarthritis, unless the person has knee osteoarthritis with a clear history of mechanical locking (not gelling, 'giving way' or X-ray evidence of loose bodies).

- Healthcare professionals should consider offering paracetamol for pain relief in addition to core treatment (exercise, advice, etc); regular dosing may be required. **Paracetamol and/or topical NSAIDs should be considered ahead of oral NSAIDs, COX-2 inhibitors or opioids.**

JAPC have discussed the recommendations in the guideline for the pharmacological management of OA and broadly agree with the NICE recommendations. A key message is that the best way to reduce harms of oral NSAIDs is to avoid their use altogether by using alternative pain management strategies. JAPC feel that topical rubifacients and glucosamine sulphate (OA knee) remain as viable options before moving on to oral NSAIDs. Many patients already receive benefit from these treatments and to remove them from our local formulary would result in an increase in use of oral NSAIDs, leading to possible hospital admissions as a result of their harms.

There is actually a lack of evidence for the effectiveness of any therapeutic intervention for the long term management of OA. In addition, recent evidence has identified that many oral NSAIDs, particularly diclofenac, cause additional CV events. As OA is a long term condition and considering the effect of placebo in managing pain, oral NSAIDs should be used with caution, only once the other, safer, options have been tried first.

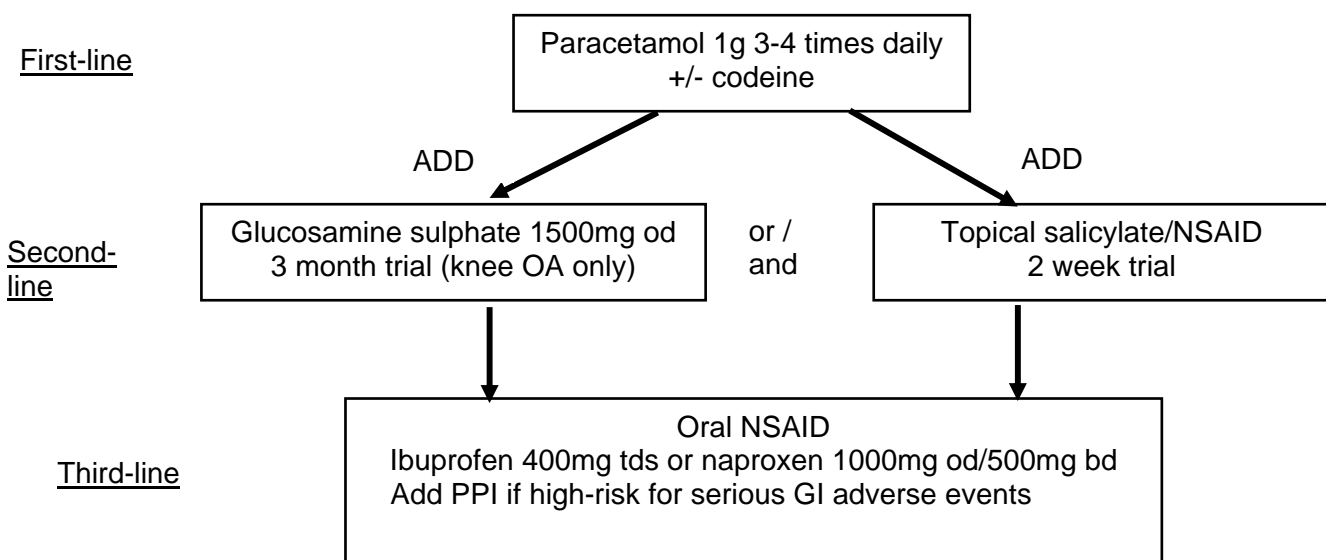
This is the recommended approach from JAPC:

First-line: Paracetamol 1g 3-4 times daily.  
Add codeine 15-30mg if necessary for flare-ups.

Second-line: add either

- Glucosamine sulphate 1500mg daily (suggested brands: Lifespan, Natrahealth, Valupak) – knee OA only.  
Three month trial necessary to assess effectiveness.
- Topical salicylate (e.g. Algesal, Transvasin) or topical NSAID (e.g. ibuprofen gel, ketoprofen gel).  
Two week trial to assess effectiveness.
- Use both if necessary.

Third-line: Consider an oral NSAID - ibuprofen 1200mg daily is first-line and naproxen 1000mg daily second-line (NB avoid enteric-coated tablets).  
Add omeprazole 20mg or lansoprazole 15mg daily if high risk for serious GI adverse events.  
This will not reduce the risk of CV or renal adverse events.  
Use of coxibs is not recommended.



### **Cold sore machine on NHS prescription**

You may have seen adverts in the national press highlighting this to the public. What actually is it?

The Virulite CS device is a handheld battery-operated device (PP3; 9V), with a clear treatment window that is held against the skin surface at the site of the cold-sore infection. The device emits pulsed 1072-nm narrowband light from two light-emitting diodes, and has an internal microprocessor that ensures consistent light intensity and duration, with a timer and automatic treatment cut-off after a 3-min treatment cycle. The end of treatment is denoted by an audible signal. The Drug Tariff price is £18.50.

There seems to be a very limited evidence base (two published trials with a total of 92 patients), and no long term safety data. We have discussed this at JAPC and the advice is that it is **not recommended for prescribing**.

### **Drug safety update**

This can be found at [www.mhra.gov.uk/drugsafetyupdate](http://www.mhra.gov.uk/drugsafetyupdate). The April issue majors on contraception and here are some of the key points.

#### **Hormonal contraceptives: *cervical cancer – latest evidence***

Further evidence suggests that long-term use of combined oral contraceptives or progestogen-only injectable contraceptives is associated with a small increased risk of cervical cancer. The level of risk returns to that for never-users within 10 years of stopping use.

A new report estimates that:

- women who use COCs for **5 years** from age 20 years have increased cumulative incidence of cervical cancer at age 50 years from **38 cases** per 10,000 (in never-users) to **40 cases** per 10,000 (i.e. an extra two cases per 10,000)
- women who use COCs for **10 years** from age 20 years have increased cumulative incidence of cervical cancer at age 50 years from **38 cases** per 10,000 (in never-users) to **45 cases** per 10,000 (i.e. an extra seven cases per 10,000).

Risk falls when COCs are stopped; after about 10 years, risk reaches the same level as that for never-users of COCs. The data suggest that the risk of cervical cancer in users of progestogen-only injectable contraceptives (i.e. Depo-Provera and Noristerat) may be similar to that for COC users.

No epidemiological data are available for the risk of cervical cancer in users of Evra▼ (a combined hormonal contraceptive patch), NuvaRing, (a combined hormonal intravaginal contraceptive), progestogen-only pills, Implanon (a progestogen-only implant), or Mirena (a progestogen-only intrauterine device).

#### **Combined hormonal contraceptives: *venous thromboembolism – update***

The risk of venous thromboembolism in users of Yasmin is in the same range as that for users of combined oral contraceptives that have low ethinylestradiol dose, including second-generation pills. The risk in users of the Evra▼ contraceptive patch may be slightly increased compared with that for users of second-generation pills.

#### **Cyproterone acetate with ethinylestradiol (co-cyprindiol): *recommended duration of use***

Most women will be able to stop cyproterone acetate with ethinylestradiol (co-cyprindiol) 3-4 months after resolution of symptoms. This should not be interpreted as stopping treatment after 3-4 months. For women with known hyperandrogenism who attend specialist clinics, co-cyprindiol may be the only effective treatment for severe symptoms. Under these circumstances, co-cyprindiol can be prescribed in the longer-term with regular specialist review.

### **Prescribing gluten-free foods**

Some gluten-free foods have Advisory Committee on Borderline Substances approval and can be prescribed for people with gluten-sensitive enteropathies, including steatorrhea due to gluten sensitivity, coeliac disease, and dermatitis herpetiformis. To confirm that this requirement has been met the prescription must be endorsed 'ACBS'.

The system is designed to provide everyday foods such as bread, pasta, pizza bases, crackers and biscuits. It is not for the supply of luxury sweet items. The quantities prescribed should be the minimum needed for a healthy diet for that individual. There are national guidelines on suitable quantities from Coeliac UK:

### Monthly minimum recommendations

Age and sex	Units per month
1-3 years	10
4-6 years	11
7-10 years	13
11-14 years	15
15-18 years	18
Male 19-59	18
Male 60-74	16
Male 75+	14
Female 19-74	14
Female 75+	12
Breastfeeding	Add 4
3 <sup>rd</sup> trimester pregnancy	Add 1
High physical activity level	Add 4

### Food chart

Item	Units
<b>400g</b> bread/rolls/baguettes	1
<b>500g</b> bread/flour/cake mix	2
<b>200g</b> sweet/savoury biscuits crackers/crispbreads	1
<b>250g</b> pasta	1
<b>2</b> pizza bases	1

A prescribing guide with more detailed information on how to provide this number of units is available at: <http://coeliac.org.uk/healthcare-professionals/168.asp> or e-mail me for a copy. To achieve a balanced diet, it is essential for the patient to include other, naturally gluten-free carbohydrates in the diet e.g. rice and potatoes. Do the quantities and items currently prescribed need a review? Do all patients prescribed gluten free foods meet the ACBS criteria for NHSD prescribing?

### Tension-type headache

There have been two reviews of this common condition recently.<sup>1,2</sup> Here is a synopsis of their recommendations.

Tension type headache (TTH) is the most common form of headache, and chronic tension-type headache (CTTH) is one of the most difficult types of headache to treat. People with infrequent episodic tension-type headache are unlikely to seek medical advice. As the frequency of tension-type headache increases so commonly does the severity of the pain and the likelihood that the patient will present for treatment. Usually patients report a mild to moderate, bilateral sensation of muscle tightness or pressure lasting hours to days and not associated with constitutional or neurological symptoms. Patients may simultaneously describe and indicate the location of the pain (the "band around the head").

### **Diagnostic criteria for tension-type headache**

- at least 10 episodes fulfilling the criteria b - d:
- headache lasting from 30 minutes to 7 days.
- headache has at least two of the following characteristics:
  - bilateral location
  - pressing/tightening (non-pulsating) quality
  - mild or moderate intensity
  - not aggravated by routine physical activity such as walking or climbing stairs
- both of the following:
  - no nausea or vomiting (anorexia may occur)
  - no more than one episode of photophobia or phonophobia
- not attributable to another disorder.

### **Infrequent episodic tension-type headache**

Diagnosed if headaches meeting the above criteria occur <1 day a month (<12 days a year) on average.

### **Frequent episodic tension-type headache**

Diagnosed if headaches occur >1 and <15 days a month (>12 and <180 days a year).

### **Chronic tension-type headache**

Diagnosed if headaches occur  $\geq$  15 days a month (180 or more days a year).

If a patient meets the criteria for tension-type headache and has a normal result on neurological examination, further diagnostic testing generally is not helpful. Manual palpation of pericranial muscles is a valuable but underused physical examination technique: pericranial muscle tenderness on palpation is the most common abnormal finding in tension-type headache, although its absence does not rule out tension-type headache. Careful funduscopic examination for papilloedema or other abnormalities is important for evaluating whether secondary headaches are present.

Therapies for TTH can be subdivided into short-term, abortive (mainly pharmacological) treatment of each attack and long-term prophylactic (pharmacological or non-pharmacological) treatments. Acute and preventative treatments can be used together. Medicine for acute headache should be used no more than 2 to 3 days per week to minimise the chance that medication overuse or 'rebound' headache will develop.

Oral aspirin 500 - 1000mg has the best evidence of effectiveness for acute attacks in RCTs. Ibuprofen 800mg and naproxen sodium 825mg are alternatives and are likely to have better GI tolerability. Evidence for paracetamol is mixed. It is probably more effective than placebo, but inferior to NSAIDs. The adjunction of caffeine (130mg or 200mg) significantly increases the efficacy of simple analgesics and ibuprofen in controlled trials. Opioids should not be used routinely to treat TTH as they increase the risk of chronic headache.

Daily preventive treatment should be considered for patients with frequent headaches or who respond poorly to abortive treatment (pain reducing treatment) alone. The best evidence of effectiveness from randomised controlled trials is for amitriptyline, usually in doses of 75 - 150mg a day. In addition to its effects on pain, amitriptyline decreases muscle tenderness. Amitriptyline also is effective for migraine prophylaxis, making it a good choice for patients who have both.

Clinical experience suggests that side effects are minimised and compliance increased when preventive treatment is started at a low dose and gradually increased until the target dose is reached. A common practice is to increase the dose at weekly intervals. Headaches naturally wax and wane, so two or three months of preventive treatment at the target dose is recommended before outcomes can be judged.

The usual goals of treatment are a reduction in the frequency and intensity of headache and improved response to abortive treatment. The optimal duration of preventive treatment is unknown. In the absence of evidence, a reasonable practice is to continue a successful preventive regimen for six months and then slowly reduce the dose while observing headache frequency. Treatment can be resumed if headaches recur.

SSRIs have, as yet, not been convincingly proved as effective as TCAs for prevention of TTH. There is solid scientific support for the usefulness of relaxation and electromyography biofeedback therapies in the management of TTH. The combination of stress management and amitriptyline ( $\leq 100\text{mg/day}$ ) or nortriptyline ( $\leq 75\text{mg/day}$ ) was more effective in patients with CTTH than either behavioural therapy or drug treatment alone.

### ***Tips for non-specialists<sup>1</sup>***

- Most patients in general care who present with headache have either migraine or tension-type headache
- The history of headache features is most important in making a diagnosis; with the exception of pericranial muscle tenderness to manual palpation, physical and neurological examinations should yield normal results in patients with tension-type headache or any abnormalities should be explained by other conditions
- If worrisome examination or historical features are present, secondary headache should be excluded with appropriate testing
- If the distinction between migraine, tension-type headache, and other primary headache is not clear, a headache diary can help to clarify the diagnosis
- Some patients with occasional headaches do not need medical treatment. Others need only simple analgesics for acute headaches. Preventive treatment should be considered when acute treatment is ineffective or overused or if headache occurs more than four times a month
- An important responsibility of the physician is to monitor medication intake to prevent overuse
- Patients who regularly use acute medication for headache more than two to three days a week or whose headaches respond poorly to treatment should be referred to a specialist.

1. BMJ 2008; 336:88-92

2. Lancet Neurol 2008; 7:70-83

## **Glycaemic targets in type 2 diabetes**

Many people with type 2 diabetes spend a lot of time, effort and money trying to keep their blood glucose down to normal or close to normal. Is there solid evidence for this approach? According to Iona Heath, clinical trial evidence has been shamelessly extrapolated across time, population subgroup, and condition.<sup>1</sup>

The results of the United Kingdom Prospective Diabetes Study (UKPDS), published in 1998, have been used to support the emphasis on tight control of blood glucose levels in type 2 diabetes. However, as McCormack and Greenhalgh have so carefully argued<sup>2</sup>, the study in fact showed no clinically important benefit from the control of blood glucose with sulphonylureas and insulin over more than 10 years. Differences were detected in process measures such as albuminuria and the progression of retinopathy, but there were no differences in the outcomes that are important to patients: renal failure, blindness, and loss of visual acuity. The only effective agent was metformin, which is undoubtedly beneficial through mechanisms that seem poorly understood and are not completely explained by the effect on blood glucose levels. This is grade A evidence (i.e. from a RCT).

A publication reporting observational data from the UKPDS trial relating measures of glucose to outcomes<sup>3</sup> is used to support tight blood glucose control in type 2 diabetes. This is grade C evidence. In the hierarchy of evidence A is more trustworthy than C.

Therapeutics letter (the Canadian equivalent of DTB) has assessed the evidence for glycaemic targets in type 2 diabetes.<sup>4</sup> They reach the following conclusions:

- A glycaemic target of <6% compared to a target of 7 to 7.9% caused increased mortality in type 2 diabetics who were at high risk of cardiovascular events.
- The optimal glycaemic target in patients with type 2 diabetes is unknown.
- Additional RCTs that test specific glycaemic targets are needed for the full spectrum of patients with type 2 diabetes.

As a recent article<sup>5</sup> entitled 'Prescribing for type 2 diabetes – not as clear cut as it seems' points out:

"It would appear that the most important exercise we should carry out with people with diabetes is to address their cardiovascular risk aggressively, treating their hypertension and raised lipids with potent 'golden age' drugs. At the same time we should render them symptom free with the contemporary antidiabetic agents we know to be safe and encourage them to have as active a physical activity programme that they can manage."

To reduce the risk of nasty things happening to people with type 2 diabetes, we need to 'lend them a hand'. Informed choice should require that patients be provided with full explanations of the likely level of benefits expressed as absolute, and not relative, risk reduction.

