

NEWSLETTER

Supporting the Derbyshire Health Community

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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 lies with a hospital consultant or a specialist. AMBER drugs are those that are initiated within a hospital/specialist setting but are suitable for shared care with a 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; the full list is available at

<http://www.derbyshirecountypct.nhs.uk/guidelines/default.asp>

The guidelines, formulary chapters, newsletters, etc can now be found via this link.

Drug	Date considered	Decision
Fentanyl patch/tablet/lozenge	March 2009	GREEN (third-line use only)
Fluticasone furoate nasal spray (Avamys)	March 2009	BROWN
Ranolazine	March 2009	BROWN
Tadalafil 2.5mg and 5mg tablets (Cialis once-a-day)	March 2009	BROWN
Targinact (oxycodone + naloxone)	March 2009	BROWN
NuvaRing	March 2009	RED
Lacosamide	February 2009	RED
Ropinirole XL	February 2009	GREEN (only on consultant recommendation)

Guidelines update

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

- Management of familial hyperlipidaemia
- Prescribing for oral thrush in babies
- Statin Policy (update)
- Oral anticoagulation
- Disulfiram shared care
- Phosphate binder shared care (Derby Hospitals)
- Liothyronine in depression shared care
- Nebulised colomycin in adults shared care (Chesterfield Royal Hospital)
- Tinzaparin in active cancer shared care (Chesterfield Royal Hospital)

You can obtain copies of these from your Medicines Management team, from me, or from the website address above.

COPD treatment algorithm

The COPD treatment algorithm (see page 8) has once again been discussed at JAPC and ratified as the recommended approach to using drugs in this difficult to treat condition. After a meeting with the respiratory consultants at Chesterfield and Derby, a consensus was reached that there is no strong evidence to support triple therapy with tiotropium + long-acting beta-agonist (LABA) + inhaled corticosteroid (ICS). In addition, there is no specific group of patients that can be identified that would be likely to benefit.

The RCT that investigated triple therapy in COPD was reported in the May 2007 issue of this newsletter. A cost effectiveness analysis of that study has now been published¹. The authors concluded that neither triple therapy nor tiotropium + salmeterol are economically attractive alternatives compared with tiotropium monotherapy. They calculated that the cost per QALY gained for triple therapy compared with tiotropium alone was Canadian \$243,180. This is approximately £133,000 per QALY, way above the NICE threshold of £20-30,000 per QALY. The use of triple therapy is a priority for audit.

Two systematic reviews and meta-analyses on the use of ICS in COPD have recently been published. The primary outcome of the first was to assess the effect on all-cause mortality at 1 year². They found no difference in all-cause mortality at 1 year or at 3 year follow-up. However, they did find an increased risk of pneumonia with ICS use (RR 1.34 [CI 1.03 to 1.75], p = 0.03). This increased risk was dose related and appeared to be greatest in patients with the lowest baseline FEV₁.

The aim of the second paper was to ascertain the risk of pneumonia with long-term ICS use³. ICS was associated with a significantly increased risk of serious pneumonia when compared with placebo (RR 1.81 [1.44 to 2.29], p<0.001) or when the combination of ICS with LABA was compared to LABA alone (RR 1.68 [1.20 to 2.34], p=0.002). They estimated that the annual number needed to harm (NNH) for serious pneumonia associated with ICS use when added to LABA was 47.

A network meta-analysis of inhaled drugs to reduce exacerbations in patients with COPD has recently been published⁴. The paper reports that inhaled corticosteroids provide no additional value in reducing exacerbations when used concurrently with LABAs unless patients have low FEV₁ (below 40% predicted). However, they conclude that in this group of patients with low FEV₁, tiotropium appears to be the most attractive choice of therapy.

An oral mucolytic is offered as an option in the treatment algorithm for those with troublesome cough and sputum for symptom relief and as an alternative to inhaled corticosteroid to reduce exacerbations. The Database of Abstracts of Reviews of Effects (DARE) has published a review⁵ of a meta-analysis of RCTs evaluating the effect of an oral mucolytic, N-acetylcysteine, on exacerbations of COPD. N-acetylcysteine was associated with a significant reduction in the odds of experiencing one or more exacerbations over 6 months compared to placebo (OR 0.49, 95% CI: 0.32 to 0.74, p=0.001). The NNT was 7. There was no significant correlation between baseline FEV₁ % predicted and the effect of N-acetylcysteine. Smoking status did not affect the efficacy of treatment but the effects may be less in patients taking ICS.

DARE comment that the authors' conclusions appear appropriate. Unfortunately with oral mucolytics we are presented with a similar scenario to the one with choice of thiazide diuretic. The drugs trialed have mainly been chlortalidone and hydrochlorothiazide, which are not easily available in the UK, so we use bendrofluazide and hope it is a class effect. With oral mucolytics the evidence is largely for N-acetylcysteine but we only have available carbocisteine and mecysteine.

1. Thorax 2008; 63:962-67
2. JAMA 2008; 300:2407-16
3. Arch Intern Med 2009; 169:219-29
4. BMC Medicine 2009; 7:2 doi:10.1186/1741-7015-7-2
5. www.crd.york.ac.uk/CRDWeb/ShowRecord.asp?ID=12007000095

Drug safety update

This can be found at www.mhra.gov.uk/Publications/Safetyguidance/DrugSafetyUpdate/index.htm

Here are some key points from the February issue.

Tibolone (Livial): *increased risk of breast cancer recurrence*

Tibolone increases the risk of breast cancer recurrence in women with a history of breast cancer. Tibolone should not be used in women with known or suspected breast cancer, or in those with a history of breast cancer.

Non-steroidal anti-inflammatory drugs: *cardiovascular risk*

Results of two recently published epidemiological studies lend support to the view that some increase in thrombotic cardiovascular risk may apply to all NSAID users, irrespective of their baseline risk, and not only to chronic users. The absolute increase in risk for 'healthy' users is very low. Current advice remains that patients should use the lowest effective dose and the shortest duration of treatment necessary to control symptoms. Overall evidence continues to indicate that naproxen is associated with a lower thrombotic risk than coxibs. For ibuprofen, no significant increase in risk has been identified for doses of up to 1200mg daily.

Information and advice for healthcare professionals:

- Two recent epidemiological studies lend support to the view that some increased cardiovascular risk may apply to all NSAID users, irrespective of their baseline risk, and not only to chronic users. However, the greatest concern relates to chronic use of high doses (especially for coxibs and diclofenac)
- Patients should use the lowest effective dose and the shortest duration of treatment necessary to control symptoms. The need for long-term treatment should be reviewed periodically.
- Overall evidence continues to indicate that naproxen is associated with a lower thrombotic risk than coxibs. For ibuprofen, no significant risk has been identified for doses of up to 1200mg daily.
- The findings from these studies do not change previous advice to support safer NSAID use that was issued in 2006 from the Commission on Human Medicines after a Europe-wide review.

Aspirin for primary prevention of CV disease

The December issue of this newsletter presented the evidence for the use of aspirin for primary prevention in people with diabetes and JAPC's recommendation that aspirin should no longer be used. The same issue also reported on the Cochrane review of primary prevention in patients with elevated blood pressure, which concluded that aspirin therapy cannot be recommended since the magnitude of benefit, a reduction in MI, is negated by harm of a similar magnitude, an increase in major haemorrhage.

JAPC has now reviewed the evidence for use of aspirin in primary prevention of CV disease in people without diabetes. There have been six RCTs and the results of these have been combined in a sex-specific meta-analysis¹. Three studies included only males, one included only females and two included both sexes.

Aspirin was associated with a statistically significant decrease in cardiovascular events in women (OR 0.88, 95% CI: 0.79 to 0.99, P<0.03) and men (OR 0.86, 95% CI: 0.78 to 0.94, P=0.01) compared with placebo.

In women, aspirin was associated with a statistically significant reduction in the occurrence of stroke (OR 0.83, 95% CI: 0.70 to 0.97, P=0.02). When stroke sub-type was investigated, aspirin was associated with a reduction in ischaemic stroke but not haemorrhagic stroke. There was no statistically significant effect on MI, cardiovascular and all-cause mortality for women.

In men, aspirin was associated with a statistically significant reduction in the occurrence of MI (OR 0.68, 95% CI: 0.54 to 0.86, P<0.001), but had no statistically significant effect on stroke overall (though there was a statistically significant increase in haemorrhagic stroke) and no effect on cardiovascular and all-cause mortality.

Aspirin therapy increased the risk of bleeding in both men and women.

These are the results presented in absolute terms.

Aspirin therapy for an average of 6.4 years results in an average absolute benefit of approximately 3 CV events prevented per 1000 women and 4 CV events prevented per 1000 men.

Aspirin therapy for an average of 6.4 years results in an average absolute increase of approximately 2.5 major bleeding events caused per 1000 women and 3 major bleeding events caused per 1000 men.

Or alternatively as NNTs and NNHs (taken from EBN²).

		RRR (CI)	NNT (CI)
Women	Major CV composite	12% (1 to 21)	322 (184 to 3870)
	Stroke	17% (3 to 30)	445 (252 to 2523)
		RRI (CI)	NNH (CI)
	Major bleeding	67% (13 to 150)	323 (145 to 1684)
		RRR (CI)	NNT (CI)
Men	Major CV composite	13% (6 to 21)	155 (98 to 363)
	MI	32% (14 to 45)	116 (80 to 266)
		RRI (CI)	NNH (CI)
	Major bleeding	71% (35 to 119)	292 (176 to 599)

JAPC agreed that there was not sufficient evidence to support the use of aspirin in primary prevention.

There should be no new prescribing and existing patients should be reviewed and be presented with the evidence and be involved in the decision on whether to stop the aspirin.

There is no evidence to support the use of clopidogrel in primary prevention as this has not been investigated in trials. Clopidogrel is not licensed for primary prevention of CV events.

1. JAMA 2006; 295:306-13
2. EBN 2006; 9:76

Use and care of spacer devices

Spacer devices are chamber devices that remove the need for co-ordination between actuation of a pressurised metered-dose inhaler (pMDI) and inhalation. They are useful for patients with poor inhalation technique, for children, for patients requiring higher doses, for nocturnal asthma, and for patients prone to oral candidiasis with inhaled corticosteroids.

There are various spacer devices available on the market. Space devices are not interchangeable; different spacers may deliver different amounts of inhaled corticosteroid, which may have implications for both safety and efficacy. It is important to prescribe a spacer device that is compatible with the pMDI prescribed (see individual Summary of Product Characteristics).

There are no official guidelines or general consensus on the practical issues of using spacer devices. A UKMi Q & A (121.1) provides some advice.¹

Should a new spacer device be primed before first use?

A spacer device does not need to be primed with the first dose from a pMDI

Should a new spacer device be washed before first use?

It is preferable to pre-wash a spacer device before using it for the first time to eliminate any electrostatic charge transferred to the spacer device from the manufacturing and packaging process.

How should a spacer device be washed?

The spacer device should be washed with a non-ionic detergent e.g. washing up liquid and left to air-dry without rinsing or wiping. The mouthpiece should be wiped clean of detergent before use.

How often should a spacer device be washed?

Most sources recommend monthly washing although this may differ from manufacturer's instructions. Alternatively the spacer device should be washed when there are visible deposits on the spacer wall.

How frequently should a space device be replaced?

The general consensus is that they should be replaced every 6-12 months. Replacement may be required earlier if the integrity of the spacer device is compromised.

Limitations

- No published evidence was found to address this question; content is based on consensus viewpoints.
- The information contained in this FAQ may differ from individual manufacturer's instructions.
- This FAQ does not review how spacer devices should be used.

1. www.nelm.nhs.uk/en/NeLM-Area/Evidence/Medicines-Q--A/What-practical-issues-need-to-be-considered-for-the-use-and-care-of-spacer-devices/

The VADT study (N Engl J Med 2009; 360:129-39)

“Once again, intensive glucose control does not benefit people with established type 2 diabetes if other cardiovascular risk factors are addressed”³.

In contrast to observational studies and much current clinical practice, RCTs attempting to show that intensive drug strategies to control blood glucose to low target levels produces a reduction in important clinical outcomes have produced disappointing results. Intensive blood glucose control may even increase risk of death¹. Ten years ago, the UKPDS RCT in newly diagnosed people with type 2 diabetes found that achieving an HbA_{1c} of 7% vs 7.9% with insulin or sulphonylureas had no statistically significant beneficial effect on all-cause mortality, macrovascular events or most microvascular events². The Veterans Affairs Diabetes Trial (VADT) was set up to compare the effects of intensive and standard glucose control on cardiovascular events.

Method

- VADT was an open-label RCT, involving 1,791 military veterans (mean age 60.4 years, 97% males) with a sub-optimal response to therapy for type 2 diabetes.
- Selection criteria included an inadequate response to maximal doses of an oral agent or insulin therapy. Exclusion criteria included a glycated haemoglobin level of less than 7.5%, the occurrence of a CV event during the previous 6 months, advanced congestive heart failure, a life expectancy of less than 7 years, and a BMI of more than 40.
- Participants were randomised to receive either intensive or standard glucose control. The goal in the intensive-therapy group was an absolute reduction of 1.5 percentage points in the glycated haemoglobin level, as compared with the standard-therapy group.
- In both study groups, patients with a BMI of 27 or more were started on two oral agents, metformin plus rosiglitazone; those with a BMI or less than 27 were started on glimepiride plus rosiglitazone. Patients in the intensive-therapy group were started on maximal doses, and those in the standard-therapy group were started on half the maximal doses.
- Before any change in oral medications, insulin was added for patients in the intensive-therapy group who did not achieve a glycated haemoglobin level of less than 6% and for those in the standard-therapy group with a level of less than 9%. Subsequent changes in medication were determined according to protocol guidelines and local assessment. The guidelines allowed for the use of any approved drug at the discretion of the investigator.
- Other modifiable CV risk factors were treated identically in the two study groups. Treatment guidelines for blood pressure and lipid control, as well as for dietary, exercise, and diabetes education, were provided to all patients.
- All patients were prescribed aspirin and a statin unless contraindicated.
- The primary outcome was the time to the first occurrence of any one of a composite of cardiovascular events, adjudicated by an end-point committee that was unaware of assignments to study groups. The cardiovascular events were documented myocardial infarction; stroke; death from cardiovascular causes; new or worsening

congestive heart failure; surgical intervention for cardiac, cerebrovascular, or peripheral vascular disease; inoperable coronary artery disease; and amputation for ischemic gangrene.

- Secondary cardiovascular outcomes included new or worsening angina, new transient ischemic attacks, new intermittent claudication, new critical limb ischemia, and death from any cause. Secondary outcomes also included microvascular complications (retinopathy, nephropathy, and neuropathy). Adverse events, including hypoglycemia, were monitored.
- The study appears to have been allocation concealed and all analyses were based on the intention-to-treat principle.
- The planned sample size of 1700 patients provided a power of 86% to detect a relative difference of 21% in the rate of the composite CV outcome.
- The study was sponsored by the Veterans Affairs Cooperative Studies Program.

Results

- A total of 1,791 patients were enrolled. The mean time since diagnosis was 11.5 years. The mean BMI was 31.3 and the mean glycated haemoglobin level at baseline was 9.4%. Hypertension was present in 72% of patients, and 40% had already had a CV event. At baseline, 52% were receiving insulin.
- The median follow-up was 5.6 years.
- The mean baseline blood pressure was 132/76 mm Hg in the two groups. After 6 years, for patients who were still in follow-up, the mean blood pressure was 125/69 mm Hg in the standard-therapy group and 127/68 mm Hg in the intensive-therapy group. In both groups, mean lipid levels improved during the study, and levels of LDL-cholesterol decreased to 2.1 mmol/L.
- The use of antiplatelet drugs increased to 91% and 94% of patients in the two groups, respectively, and statin use increased to 83% and 86% of patients, respectively. Weight and BMI were significantly greater (by 9 lb [4 kg] and 1.5, respectively; $P=0.01$) in the intensive-therapy group after treatment.
- At 3 months, median glycated haemoglobin levels had decreased in both groups and had stabilised at 6 months, with a level of 8.4% in the standard-therapy group and 6.9% in the intensive therapy group. This result achieved the pre-specified goal of an absolute between-group difference of 1.5 percentage points.
- No significant benefit in the time to the first occurrence of a cardiovascular event was observed in the intensive-therapy group (hazard ratio, 0.88; 95% confidence interval [CI], 0.74 to 1.05; $P=0.14$). There was no evidence that the effect of treatment varied according to either insulin status at baseline or the previous occurrence of a CV event ($p=0.37$ and $p=0.92$, respectively).
- There were no significant differences in individual components of the primary and secondary outcomes.
- There was no significant difference in death from CV causes or death from any cause.
- No difference was observed between the two groups for microvascular complications (ophthalmic, nephropathic or neuropathic).
- The most common adverse event was hypoglycaemia, with significantly more episodes in the intensive-therapy group than in the standard-therapy group, including episodes with symptoms (1333 vs 383 per 100 patient-years), impaired consciousness (9 vs 3), and complete loss of consciousness (3 vs 1) [all $p<0.001$].

Discussions/implications

- “Once again, intensive glucose control does not benefit people with established type 2 diabetes if other cardiovascular risk factors are addressed”³.
- The authors of VADT comment “appropriate management of hypertension, dyslipidaemia, and other cardiovascular risk factors appears to be the most effective approach to preventing cardiovascular morbidity and mortality”.
- This is echoed in the NPC review³ “the VADT study provides still further evidence that intensive control of blood glucose does not help people with type 2 diabetes who have attended to other risk factors”.
- VADT very well illustrates the law of diminishing returns and provides strong support for following the diabetes ‘hand’.
- The NPC recommends that health professionals and people with type 2 diabetes should prioritise lifestyle interventions (losing weight, healthy diet, stopping smoking if relevant), blood pressure control, taking a statin, aspirin if CV disease is present, and metformin. Individual targets should be agreed for blood glucose. Interventions to control blood glucose intensively appear to add little and attempts to achieve very tight control of blood glucose may do more harm than good³.

- VADT does not address the question as to whether early intensive control of HbA_{1c} improves clinical outcomes, but UKPDS² recruited newly-diagnosed patients and found that intensive control conferred limited microvascular benefits and no macrovascular benefits.
- An article that reviews the evidence for control of blood glucose level in type 2 diabetes states that it is time to challenge conventional wisdom⁴. The author advises “Physicians should use drugs to control blood glucose level only if demonstrated through RCTs to be both safe and efficacious in reducing important clinical outcomes (e.g. metformin) or if needed for symptomatic relief. I would not recommend trying to achieve HbA_{1c} levels lower than 7% unless it can be done through non-pharmacologic means and/or metformin therapy. Prudence would dictate not using multiple oral agents at this time.”

1. N Engl J Med 2008; 358:2545-59
2. Lancet 1998; 352:837-53
3. www.npci.org.uk/blog/?p=258
4. Arch Intern Med 2009; 169: 150-54

Clopidogrel and PPIs

Concurrent use of proton pump inhibitors (PPIs) by patients taking clopidogrel after discharge from hospital following treatment for acute myocardial infarction (MI) may be associated with an increased risk of re-infarction, according to the results of a retrospective population-based case control study¹. 5.7% of patients were re-admitted with acute MI in the 90 days after discharge. The risk of re-infarction was increased by 27% (adjusted odds ratio 1.27; [95% confidence interval 1.03 to 1.57]) in those taking PPIs.

The authors of the study estimate that 5% to 15% of early re-admissions for MI could be due to an interaction between clopidogrel and PPIs. Pantoprazole and histamine H₂-receptor antagonists did not increase the risk of re-infarction. The authors speculate that their findings are supported by data indicating that all PPIs (except pantoprazole) reduce the metabolic activation of clopidogrel via inhibition of cytochrome P450 isoenzyme 2C19. Data on the individual risk associated with other PPIs were not presented.

Observational studies like this cannot prove cause and effect. In reality they set a hypothesis. Bias and confounding are always possible. Differences in the demographics of cases and controls are acknowledged and have been adjusted for. However it is not known whether there were any differences between the two groups in other risk factors that could have influenced the risk of MI, such as smoking status, hypertension, lipid profile, and OTC use of anti-platelet drugs or statins.

The US Food and Drug Administration (FDA) has begun a safety review of clopidogrel in view of a number of reports suggesting that it may be less effective in some patients because of genetic differences in how clopidogrel is metabolised or concurrent use of potentially interacting drugs. The FDA note that there have been some studies that do not support an interaction between clopidogrel and PPIs. They expect to take several months to publish the results of their review and in the interim advise that:

- Healthcare providers should continue to prescribe and patients should continue to take clopidogrel as directed, because clopidogrel has demonstrated benefits in preventing blood clots that could lead to a heart attack or stroke.
- Healthcare providers should re-evaluate the need for starting or continuing treatment with a PPI, including OTC preparations, in patients taking clopidogrel.
- Patients taking clopidogrel should consult with their healthcare provider if they are currently taking or considering taking a PPI.

No action is currently being taken by the European Medicines Evaluation Agency or the Medicines and Healthcare products Regulatory Agency.

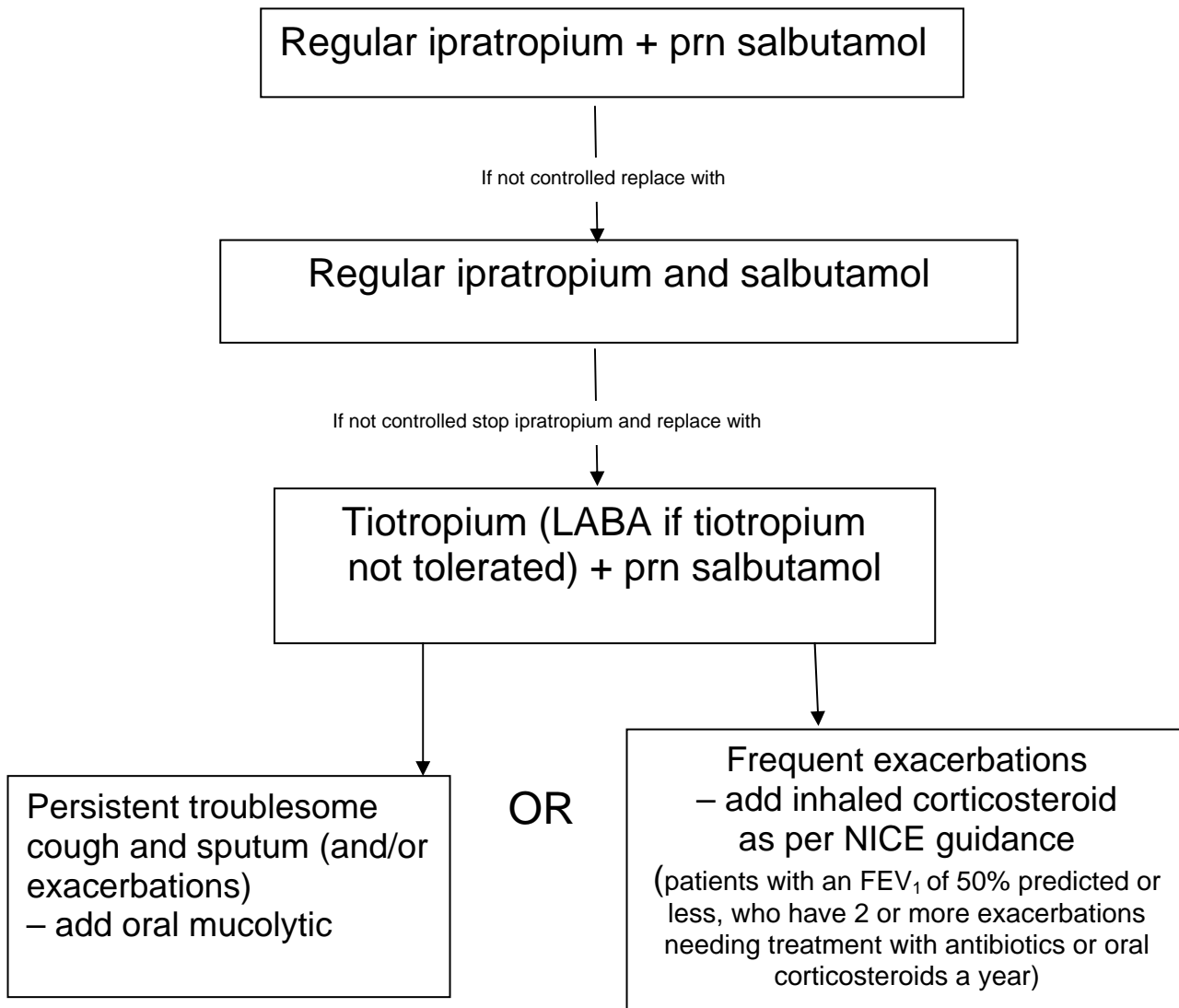
The first question perhaps should be ‘is clopidogrel still indicated for this patient?’ (see [JAPC clopidogrel guidance](#) – section 2, ACS). The second question would then be ‘does this patient really need a PPI?’ Is there a clear indication for a PPI or is it being given as routine prophylaxis? Report suspected adverse drug reactions with clopidogrel to the Medicines and Healthcare products Regulatory Agency ([MHRA](#)) through the [Yellow Card Scheme](#).

1. Can. Med. Assoc. J., Jan 2009; doi:10.1503/cmaj.082001

Algorithm for drug use in COPD

Airflow obstruction must be present before using bronchodilators

When prn salbutamol is insufficient -



There is lots of other useful advice in the full Derbyshire [COPD guideline](#).