NHS Lincolnshire

Prescribing and Clinical Effectiveness Bulletin

Volume 4; Number 2 **March 2010**

What's new this month:

- **Nicotinic acid/ laropiprant modified release tablets (Tredaptive) are reviewed (see page 3)**
- **The role of ezetimibe (Ezetrol) is clarified (see page 4)**
- **Saxagliptin (Onglyza) is not approved for the treatment of type 2 diabetes mellitus (see page 7)**
- **Ketoprofen/omeprazole MR capsules (Axorid) are not approved (see page 9)**
- **New evidence reinforces the role of varenicline for smoking cessation in people with stable cardiovascular disease (see page 9)**
- **Does higher usage of low cost statins correlate with poorer achievement in cholesterol quality markers for secondary prevention? (see page 10)**

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This bulletin has been created specifically to convey details of decisions taken at the Prescribing and Clinical Effectiveness Forum (PACEF) to all stakeholders across the Lincolnshire Healthcare Community in both primary and secondary care. Back issues of the *PACE Bulletin* and other PACEF publications are available through the NHS Lincolnshire website (www.lpct.nhs.uk). Click on 'Commissioning' and follow the links to PACEF.

SUMMARY OF PACEF DECISIONS: JANUARY 2010 UPDATE

Drug	Indication(s)	Traffic Light Status
Ezetimibe 10mg tablets (Ezetrol) *Reminder*	Licensed for the treatment of primary (heterozygous-familial or non-familial) hypercholesterolaemia and homozygous sitosterolaemia.	GREEN Restricted role subject to NICE CGs 67, 71 and 87 (see PACEF recommendations on page 4)
Ezetimibe/ simvastatin tablets 10mg/20mg, 10mg/40mg, 10mg/80mg (Inegy) *Reminder*	Licensed for the treatment of homozygous familial hypercholesterolaemia, primary hypercholesterolaemia and mixed hyperlipidaemia in patients stabilised on the individual components in the same proportion or for patients not controlled by statin alone.	RED-RED
Ketoprofen/omeprazole 100mg/20mg and 200mg/20mg modified release capsules (Axorid)	Licensed for the symptomatic treatment of rheumatoid arthritis, ankylosing spondylitis and osteoarthritis in patients with a previous history (or at risk) of	RED-RED

	developing NSAID associated duodenal ulcers or gastroduodenal erosion in whom continued treatment with a NSAID is essential.	
Nicotinic acid/ laropiprant modified release tablets (Tredaptive)	Licensed for the treatment of dyslipidaemia either in combination with statins or as monotherapy when statins are contraindicated or not tolerated.	AMBER For specialist initiation only; no shared care guideline is required.
Saxagliptin tablets 5mg (Onglyza)	Licensed for the treatment of type 2 diabetes mellitus (DM), either in combination with metformin or a sulfonylurea or a thiazolidinedione (glitazone) when monotherapy with these alternative agents (in combination with diet and exercise) does not provide adequate glycaemic control.	RED-RED
Sitagliptin tablets 100mg (Januvia) *Reminder*	Licensed for dual therapy with metformin or a glitazone for type 2 diabetes inadequately controlled by diet, exercise and either metformin or a glitazone alone; or with a sulfonylurea in patients with an intolerance or contraindication to metformin, inadequately controlled by maximal tolerated doses of sulfonylurea alone. Also licensed for triple therapy with metformin and a sulfonylurea for type 2 diabetes inadequately controlled by dual therapy.	GREEN N.B. Can be considered at step two in combination with either metformin or a sulfonylurea. Can also be considered at step three in combination with metformin and a sulfonylurea (see text for details).
Vildagliptin tablets 50mg (Galvus) *Reminder*	Licensed for the treatment of type 2 diabetes in combination with: (1) metformin, in patients inadequately controlled by maximal tolerated dose of metformin alone; (2) a sulfonylurea, in patients with an intolerance or contraindication to metformin inadequately controlled by maximal tolerated dose of sulfonylurea; (3) a glitazone, in patients with insufficient glycaemic control and for whom the use of glitazone is appropriate	RED-RED
Vildagliptin/metformin tablets (Eucreas) 50mg/850mg or 50mg/1000mg *Reminder*	Licensed for the treatment of type 2 diabetes in patients inadequately controlled by maximal tolerated dose of metformin alone or who are already treated with a combination of vildagliptin and metformin prescribed as separate components.	RED-RED

RED-RED: This signifies that a product is **not recommended** for prescribing in **either** primary or secondary care. All new products are classified as RED-RED pending assessment by PACEF.
RED: This signifies that a product has been approved for use within secondary care, tertiary care or a primary care hosted specialist service only and **should not be routinely prescribed in primary care**. RED drugs may be used within ULHT or LPFT subject to approval for use within each Trust. ULHT and LPFT reserve the right to determine whether or not RED drugs will be used within their Trusts. RED classification does not automatically signify that a drug will be available within secondary/tertiary care.
AMBER: This signifies that a drug has been approved for use in primary care **subject to specialist initiation; a shared care guideline (SCG) may also be required**. The main purpose of the SCG will be to clearly define both specialist and GP responsibilities. Not all AMBER drugs that require SCGs are currently covered by formal documents; PACEF are working to rectify this.
GREEN: This signifies a product that is **approved for initiation in either primary or secondary care within licensed indications**. Specialist initiation and shared care guidelines are not considered necessary.

REPORTING INCIDENTS TO THE NATIONAL PATIENT SAFETY AGENCY (NPSA)
The NPSA are keen to encourage the anonymous reporting of patient safety errors and systems failures both from healthcare professionals and patients. The National Reporting and Learning System (NRLS) has been set up to facilitate this process. Healthcare professionals can either report patient safety incidents through their local risk management scheme or directly into the NRLS using the eForm on the NPSA website. Please access www.npsa.nhs.uk for more information. **All healthcare professionals are encouraged to report incidents, errors and systems failures; the aim is to help the NHS to learn from things that go wrong.**

NEW DRUG ASSESSMENT: NICOTINIC ACID/ LAROPIPRANT MODIFIED RELEASE TABLETS (TREDAPTIVE)

Tredaptive is a new modified release combination product containing nicotinic acid and laropiprant. It is licensed for the treatment of dyslipidaemia and can be used either in combination with statins or as monotherapy when statins are contraindicated or not tolerated. Each modified release tablet contains 1000mg of nicotinic acid and 20mg of laropiprant. The inclusion of laropiprant in the formulation is to reduce the incidence of cutaneous flushing, the most common side effect associated with the use of nicotinic acid. Cutaneous flushing with nicotinic acid is caused by the release of prostaglandin D2 in the skin and mediated by the DP1 receptor. Laropiprant is a potent selective inhibitor of DP1 and reduces the incidence of cutaneous flushing without compromising the lipid modulating action of the nicotinic acid component.

PACEF reviewed both of the key randomised controlled trials; both were of short duration. In the first, Tredaptive (1g/20mg) was compared head-to-head with 1g nicotinic acid MR tablets (Niaspan) and demonstrated similar effects on lipid levels and a much lower incidence of moderate, severe or extreme flushing. In the second trial, Tredaptive and statin monotherapy was compared to Tredaptive/statin combination therapy with combination therapy demonstrating significant improvements in lipid profile compared to monotherapy. Data from these trials suggest that Tredaptive has a beneficial effect on lipid profiles, producing significant reduction in both total cholesterol (TC) and LDL- C; reduction in triglycerides levels (TGs) and increased HDL-C were also observed. Previous studies have established that increasing levels of HDL-C in addition to lowering LDL-C has a beneficial effect in terms of reducing CV risk. The overall effects of the different classes of lipid regulating drugs are summarized in the table below:

Drug class	**LDL-C % change - ↓**	**TG % change ↓**	**HDL-C % change ↑**
Statins	18 to 55	7 to 30	5 to15
Nicotinic acid	5 to 25	20 to 50	15 to 35
Fibrates	5 to 20	20 to 50	10 to 20
Ezetimibe	17 to 22	4 to 11	2 to 5
Bile acid sequestrants	15 to 30	No change or increase	3
Omega 3 fatty acids	No change or increase	20 to 50	No change or increase

NICE Clinical Guideline 71: *Familial hypercholesterolaemia* (August 2008) recommends nicotinic acid for specialist initiation only where first line statins, second line ezetimibe and third line bile acid sequestrants have proven insufficient or poorly tolerated. NICE CG67 *Lipid modification* (May 2008) does not recommend nicotinic acid for primary prevention of cardiovascular disease; a limited role in secondary prevention of CVD is recognised in people unable to tolerate statins. Neither Tredaptive nor nicotinic acid MR tablets (Niaspan) are licensed for the primary or secondary prevention of cardiovascular disease, largely due to the lack of outcome data. NICE CG87 *Type 2 diabetes* (May 2009) does not recommend nicotinic acid preparations routinely, although acknowledges that there may be a role in those intolerant of other therapies with more extreme disorders of lipid metabolism.

A cost comparison reveals that Tredaptive is expensive in comparison to other lipid regulating drugs, but is currently lower in cost that Niaspan (see below):

Drug	Daily dose range	Cost (£)pa
Tredaptive (1g/20mg)	2 tablets daily	£435
Nicotinic acid 1000mg prolonged release (Niaspan)	2 tablets daily	£497
Bezafibrate 400mg modified release (Bezalip Mono)	1 tablet daily	£101
Ciprofibrate 100mg (Modalim)	1 tablet daily	£230
Fenofibrate 200mg (Lipantil Micro)	1 capsule daily	£185
Gemfibrozil 600mg tabs	1 tablet twice daily	£154
Colestyramine Questran 4g sachets (Questran)	3-6 sachets daily	£240-480
Colestyramine 4g sachets (generic)	3-6 sachets daily	£351-702
Colesevelam 625mg tabs (Cholestagel)	4-6 tablets daily	£720-1,080
Colestipol 5g granules	5-30g daily	£183-1098
Ezetimibe 10mg (Ezetrol)	1 tablet daily	£342

PACEF Recommendation:

PACEF acknowledge a limited role for nicotinic acid preparations in line with recent NICE CGs. However, poor tolerability has often compromised its use in clinical practice. Trial evidence suggests that the addition of laropiprant significantly reduces the incidence of cutaneous flushing without impairing the lipid modifying capacity of the nicotinic acid component. Tredaptive MR tablets are also lower in cost than nicotinic acid MR tablets (Niaspan). As a result of this Tredaptive is designated AMBER for specialist initiation only where first line statins, second line ezetimibe and third line bile acid sequestrants have proven insufficient or poorly tolerated. Ongoing studies on the significance of increasing HDL-C may redefine the role of nicotinic acid in the future.

CLARIFICATION OF THE ROLE OF EZETIMIBE (EZETROL)

As part of their contribution to our assessment of Tredaptive, local cardiologists expressed their concern over the increasing use of ezetimibe monotherapy initiated in Lincolnshire primary care. Local prescribing figures also reveal significant annual growth. Concern has also arisen over the inappropriate use of statin/ezetimibe combination therapy where a second line higher potency statin might have proven more effective and less expensive. It is the purpose of this feature to clarify the role of ezetimibe from both national and local guidance in order to minimize inappropriate use.

Summary of Local and National Guidance

Prescribers are reminded of NICE guidance and standard PACEF advice on the role of ezetimibe both as monotherapy and in combination with statins. It is also emphasized that **ezetimibe is only licensed for the treatment of primary (heterozygous-familial or non-familial) hypercholesterolaemia and homozygous sitosterolaemia. Where statins are indicated and tolerated it is almost always more effective and cost-effective to use a statin (even high-cost high-potency branded statins) than to use statin and ezetimibe combination therapy or ezetimibe monotherapy (see table below).**

NICE CG67 *Lipid modification: Cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease* (May 2008)

- Ezetimibe (Ezetrol) is not licensed for either primary or secondary prevention of cardiovascular disease, although it should be considered in those with primary hypercholesterolaemia.

NICE CG 71: *Familial hypercholesterolaemia – Identification and management of familial hypercholesterolaemia* (August 2008)

- Ezetimibe is an option for adults with heterozygous familial hypercholesterolaemia (FH) if statins are contraindicated or not tolerated.
- Statin and ezetimibe combination therapy (prescribed as separate components) is an option for adults with heterozygous FH if TC or LDL-C concentrations are not appropriately controlled with statins alone.

PACEF Comment:
Prescribers are reminded that statin and ezetimibe combination therapy is only indicated in adults with heterozygous FH where second line statins (even high-cost high-potency statins) have failed to adequately control TC or LDL-C.

NICE CG87 *Type 2 diabetes – The management of type 2 diabetes* (May 2009)

- More intensive statin therapy (i.e. simvastatin 80mg) or the addition of ezetimibe is advocated if there is existing or newly diagnosed CV disease or increased albumin excretion rate. HDL-C should not exceed 1.4mmol/l; targets of 4mmol/l (TC) and 2mmol/l (LDL-C) are advocated.

PACEF Recommendations: Updated Advice on Ezetimibe

Ezetimibe monotherapy in primary (heterozygous-familial or non-familial) hypercholesterolaemia

Use simvastatin first line and aim to achieve at least 50% reduction of LDL-C concentration from baseline. High-intensity statins are recommended, increased to the maximum licensed or tolerated dose. NICE define 'higher intensity statins' as those used in doses that produce greater cholesterol lowering than simvastatin 40mg, for example simvastatin 80mg and higher doses of rosuvastatin and atorvastatin. Alternative statins should be tried and found to be poorly tolerated before ezetimibe monotherapy can be considered; ezetimibe monotherapy is not as effective in terms of TC and LDL-C lowering as even a low dose of simvastatin (see table below). Ezetimibe is also a black triangle drug.

Ezetimibe and statin combination therapy in primary (heterozygous-familial or non-familial) hypercholesterolaemia

If high intensity statins at maximum licensed or tolerated doses do not achieve sufficient LDL-C reduction from baseline, consider ezetimibe and statin combination therapy prescribed as separate components. An ezetimibe and simvastatin combination should be preferred. Co-prescribing of high-cost, high-potency statins (i.e. rosuvastatin or atorvastatin) with ezetimibe is prohibitively expensive and should be reserved for exceptional circumstances. Where exceptionally high TC or LDL-C reductions are required, a combination of ezetimibe and simvastatin 80mg should be considered. A fixed dose combination formulation of ezetimibe and simvastatin (Inegy) is available in a variety of strengths, but is significantly more expensive than separate components and should not be prescribed. Designation: RED-RED. Statin and ezetimibe combination therapy is only indicated in adults with heterozygous

FH where second line statins (even high-cost high-potency statins) have failed to adequately control TC or LDL-C.

Ezetimibe in the primary prevention of Coronary Heart Disease (CHD)

NICE TA 94 and CG 67 recommend statin therapy first line as part of the management strategy for the primary prevention of CVD in adults who have a 20% or greater 10-year risk of developing CVD. Simvastatin 40mg is recommended first line. NICE CG 67 does not recommend targets for TC or LDL-C for people treated with a statin for primary prevention. There are no clinical trials in primary prevention that have evaluated the relative and absolute benefits of cholesterol lowering to different TC and LDL-C targets and target chasing is not recommended within this context. Ezetimibe is not licensed for the primary prevention of CHD and no published cardiovascular outcomes data is available. As a result of this, there should be very little need to prescribe ezetimibe within this context except in the circumstances already defined for the treatment of primary (heterozygous-familial or non-familial) hypercholesterolaemia.

Ezetimibe in the secondary prevention of CHD

Prescribers are reminded that ezetimibe is not licensed for secondary prevention of CHD and that no cardiovascular outcomes data exists. If ezetimibe is being considered within this context, it should be as a last resort and utilized as recommended below in standard PACEF advice on the use of statins in the secondary prevention of CHD.

Standard PACEF advice on the use of statins and ezetimibe in the secondary prevention of cardiovascular disease

- **Statin therapy is recommended for adults with clinical evidence of CVD.**
- **Treatment for secondary prevention of CVD should be initiated with simvastatin 40mg. If there are potential drug interactions, or simvastatin 40mg is contraindicated, an alternative low-cost preparation such as pravastatin should be chosen. If simvastatin 40mg is not tolerated, a lower dose or pravastatin should be chosen.**
- **Targets of 4mmol/litre (TC) and 2mmol/litre (LDL-C) have been endorsed by NICE as an aspiration, but achievement is not an absolute necessity.**
- **If the patient does not reach target on simvastatin 40mg, increase the dose to 80mg. If the patient does not reach the 4mmol/l and 2mmol/l targets on simvastatin 80mg (over half of patients will not), reduce aspiration to the minimum audit standard and QOF target of 5mmol/l (TC).**
- **Maintain the patient on the dose of simvastatin that has either reached the 4 and 2mmol/l targets or the minimum audit standard of 5mmol/l (TC). Only consider higher-cost, higher-potency statins in those patients that remain above the minimum audit standard of 5mmol/l (TC) despite taking simvastatin 80mg or who are intolerant to simvastatin and pravastatin or have contra-indications or potential interactions.**
- **Remember that high-cost high-potency statins like atorvastatin and rosuvastatin are effective, but have emerged from NICE cost-effectiveness evaluations as not cost-effective in most patients. As a result of this, their use for secondary prevention of CVD should be restricted to the exceptional circumstances outlined above. The role of atorvastatin in acute coronary syndrome (ACS) has been endorsed by NICE as cost-effective but is advocated by PACEF as second line after simvastatin 80mg.**
- **Fibrates, nicotinic acid and anion exchange resins may be considered for secondary prevention of CVD in people unable to tolerate statins. Ezetimibe may be appropriate within licensed indications (i.e. primary hypercholesterolaemia).**
- **If unlicensed statin and ezetimibe combination therapy is contemplated in secondary prevention of CVD it should only be where second line high-potency statins (even high-cost high-potency statins) have failed to adequately control TC or LDL-C.**

Cost Comparison and Percentage Reductions in LDL Cholesterol and Total Cholesterol

Statin	Daily Dose	28 day cost	Percentage reduction in LDL-C	Percentage reduction in total cholesterol
Atorvastatin	10mg	£13.00	37%	32%
Atorvastatin	20mg	£24.64	43%	36%
Atorvastatin	40mg	£24.64	49%	42%
Atorvastatin	80mg	£28.21	55%	47%
Pravastatin	40mg	£2.96	29%	29%
Rosuvastatin	5mg	£18.03	38%	33%
Rosuvastatin	10mg	£18.03	43%	37%
Rosuvastatin	20mg	£26.02	48%	40%
Simvastatin	**40mg**	**£1.38**	**37%**	**31%**
Simvastatin	80mg	£2.96	42%	35%
Ezetimibe	10mg	£26.31	17- 22%	12-13%

(Prices quoted are from the *Drug Tariff*, February 2010)

NEW DRUG ASSESSMENT: SAXAGLIPTIN 5MG TABLETS (ONGLYZA)

Saxagliptin (Onglyza) is the third dipeptidyl peptidase 4 (DDP- 4) inhibitor (or gliptin) to be launched in the UK. It is licensed for the treatment of type 2 diabetes mellitus (DM), either in combination with metformin or a sulfonylurea or a thiazolidinedione (glitazone) when monotherapy with these alternative agents (in combination with diet and exercise) does not provide adequate glycaemic control.

The evidence base for saxagliptin comes from a series of six clinical trials. There is randomised controlled trial (RCT) evidence that saxagliptin is effective at lowering HbA_{1c} levels from baseline when used either as monotherapy (unlicenced) or in combination with metformin, a sulfonylurea or a glitazone. There is one 18 week comparative study against sitagliptin that demonstrates non-inferiority of saxagliptin to sitagliptin in terms of reduction in HbA_{1c} levels. This study also reported similar side effect profiles for both agents; a small decrease in bodyweight was reported for both treatment groups. Pooled results from saxagliptin clinical trials reveal that the most common adverse effects are increased upper respiratory and urinary tract infections, gastroenteritis, sinusitis headache and vomiting. This is a similar profile to the two other gliptins. All of the studies reviewed were short-term (18 to 24 weeks) and, in common with both sitagliptin and vildagliptin, there is no long-term safety or outcome data available at present.

A cost comparison reveals the following:

Drug	**Daily dose range**	**Cost (£) pa**
Saxagliptin (Onglyza)	5mg once daily	£410.80
Sitagliptin (Januvia)	100mg once daily	£432.38
Vildagliptin (Galvus)	50mg twice daily(with metformin or glitazone)	£412.88
Vildagliptin (Galvus)	50mg once `daily (with sulfonylurea)	£206.44
Vildagliptin/metformin (Eucreas) 50mg/850mg or 50mg/1000mg	50mg twice daily (plus 850mg or 1000mg metformin twice daily)	£385.36

Saxagliptin has been competitively priced and is currently marginally cheaper than the market leader sitagliptin.

PACEF Recommendations: Updated advice on DPP-4 inhibitors

DPP-4 inhibitors are advocated by NICE at both steps 2 and 3 of the Clinical Guideline for type 2 diabetes. At step 2 they should be considered in combination with first line metformin in patients at significant risk of hypoglycaemia (where a sulfonylurea might be problematic), people living alone or in those for whom a sulfonylurea is contraindicated or not tolerated. Alternatively, they should be considered in combination with sulfonylurea monotherapy in patients unable to tolerate metformin or for whom metformin is contraindicated. At step 3 sitagliptin can be considered as part of triple therapy with metformin and a sulfonylurea when control of blood glucose remains or becomes inadequate and insulin is unacceptable or inappropriate.

There are currently three DPP-4 inhibitors available in the UK, sitagliptin (Januvia), vildagliptin (Galvus) and saxagliptin (Onglyza); vildagliptin is also available in combination with metformin (Eucreas). PACEF have assessed all three of these drugs and have considered NICE CG87. NICE reviewed all clinically relevant trials involving sitagliptin and vildagliptin and concluded that DPP-4 inhibitors were non-inferior to sulfonylureas (specifically glipizide) and glitazones (pioglitazone and rosiglitazone) in terms of reduction in HbA1c. PACEF considered a head-to-head study comparing sitagliptin and saxagliptin and accepted broad equivalence in terms of both HbA1c reduction and side effect profile.

No cases of *severe* hypoglycaemia have been reported in any of the trials for the gliptins; this is the basis for the recommendation that DPP-4 inhibitors should be considered in people at risk of hypoglycaemia. DPP-4 inhibitors have also been found not to cause weight gain in most cases, although the lack of long-term safety and outcomes data remains a concern.

In a recent Cochrane review an increase in all-cause infections was reported with DPP-4 inhibitors and it was recommended that their use should be avoided in patients with a history of recurrent urinary tract infections. This is equally relevant to saxagliptin. DPP-4 inhibitors also contribute to T-cell activation which can compromise immune function.

NICE have supported a role for DPP-4 inhibitors in both dual and triple therapy. At present, sitagliptin is the only DPP-4 inhibitor licensed for *both* of these indications. In addition, vildagliptin is contra-indicated in congestive heart failure (NYHA class III-IV) and should only be prescribed with caution in CHF NYHA class I-II. This renders the use of vildagliptin as a possible alternative to the glitazones potentially problematic. There have also been rare reports of liver dysfunction with vildagliptin; Liver Function Tests (LFTs) should be monitored before initiating treatment and three monthly for the first year; LFTs should be checked periodically therafter.

Saxagliptin offers no advantage to sitagliptin other than a marginally lower price. In common with vildagliptin it does not currently hold a license for triple therapy. As a result of this, PACEF confirm that sitagliptin (Januvia) is GREEN subject to NICE initiation criteria and remains the DPP-4 inhibitor of choice; vildagliptin (Galvus), vildagliptin/metformin (Eucreas) and saxagliptin (Onglyza) are all designated RED-RED at present, but will be subject to regular review as licensing changes.

Prescribers are reminded that all gliptins are contra-indicated in moderate to severe renal impairment.

RAPID DRUG ASSESSMENT: KETOPROFEN/OMEPRAZOLE MODIFIED RELEASE CAPSULES (AXORID)

Ketoprofen/omeprazole modified release (MR) capsules are licensed for the symptomatic treatment of rheumatoid arthritis, ankylosing spondylitis and osteoarthritis in patients with a previous history (or at risk) of developing NSAID associated duodenal ulcers or gastroduodenal erosion in whom continued treatment with a NSAID is essential. Both 100mg/20mg and 200mg/20mg strengths are available.

In October 2007, the Medicines and Healthcare products Regulatory Agency (MHRA) highlighted concerns around the gastrointestinal safety of some NSAIDs, including ketoprofen. In response to safety concerns, prescribing of ketoprofen in Lincolnshire has declined significantly in recent years and current use remains low. NICE CG 59: *Osteoarthritis: The care and management of osteoarthritis in adults (February 2008)* recommends that, as the analgesic effect of different NSAIDs is similar, consideration should be given to their potential gastrointestinal, renal and cardio toxicity when selecting an appropriate treatment.

PACEF Recommendation:
Due to safety concerns highlighted by the MHRA, PACEF were unable to endorse prescribing of the combination ketoprofen/omeprazole MR capsule formulation Axorid. Designation: RED-RED. Prescribers should consider low dose ibuprofen first line whenever an NSAID is indicated. Naproxen represents a suitable second line alternative, although GI risk is higher. Diclofenac is not an appropriate first line choice due to an increased thrombotic risk on a scale comparable to the risk of coxibs; particular caution should be exercised in those with cardiovascular disease. Similar concerns exist around meloxicam. Prescribing of NSAIDs of higher GI risk (e.g. ketoprofen, piroxicam) should be kept to a minimum. All repeat and ongoing oral NSAID and Cox-2 inhibitor prescribing in people aged 55 and over should be supported with a concurrent PPI. Either generic lansoprazole capsules (recommended dose 15mg to 30mg daily) or generic omeprazole capsules (recommended dose 20mg daily) should be prescribed. These recommendations do not extend to acute or infrequent scripts.

NEW TRIALS IN BRIEF

EFFICACY AND SAFETY OF VARENICLINE FOR SMOKING CESSATION IN PATIENTS WITH CARDIOVASCULAR DISEASE

This is a randomised controlled trial (RCT) that compared the safety and efficacy of varenicline (1mg twice daily for 12 weeks) with placebo for smoking cessation in 714 smokers with stable cardiovascular disease. The continuous abstinence rate was higher for varenicline than placebo during weeks 9 through 12 and weeks 9 through 52 (19.2% vs. 7.2%). There were no significant differences in cardiovascular (CV) mortality, all cause mortality, CV events or serious adverse events. The discontinuation rate as a result of adverse events was higher in the varenicline group (9.6% vs. 4.3%).

PACEF Comment:
This study provides reassurance around the use of varenicline in patients with stable cardiovascular disease and suggests that the risk of continuing to smoke is likely to outweigh the risk relating to the documented CV side effects of varenicline.

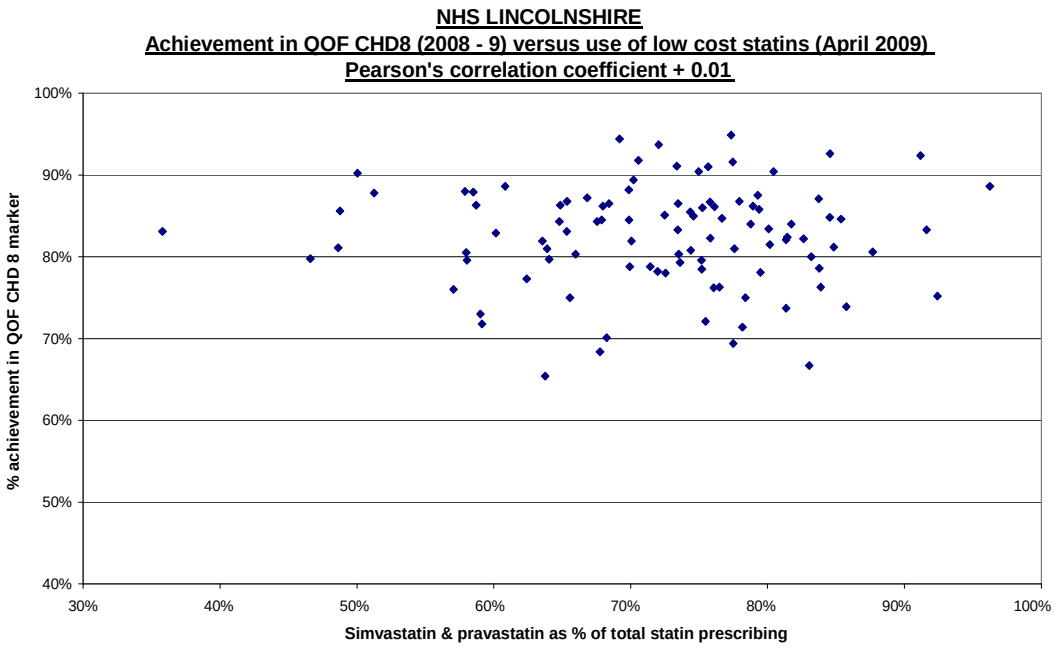
Reference: Rigotti NA et al. Efficacy and safety of varenicline for smoking cessation in patients with cardiovascular disease: a randomised trial. *Circulation* 2010 published online before print January 4 2010, doi:10.1161/ CIRCULATIONAHA. 109.869008

DOES HIGHER USAGE OF LOW COST STATINS CORRELATE WITH POORER ACHIEVEMENT IN CHOLESTEROL QUALITY MARKERS FOR SECONDARY PREVENTION?

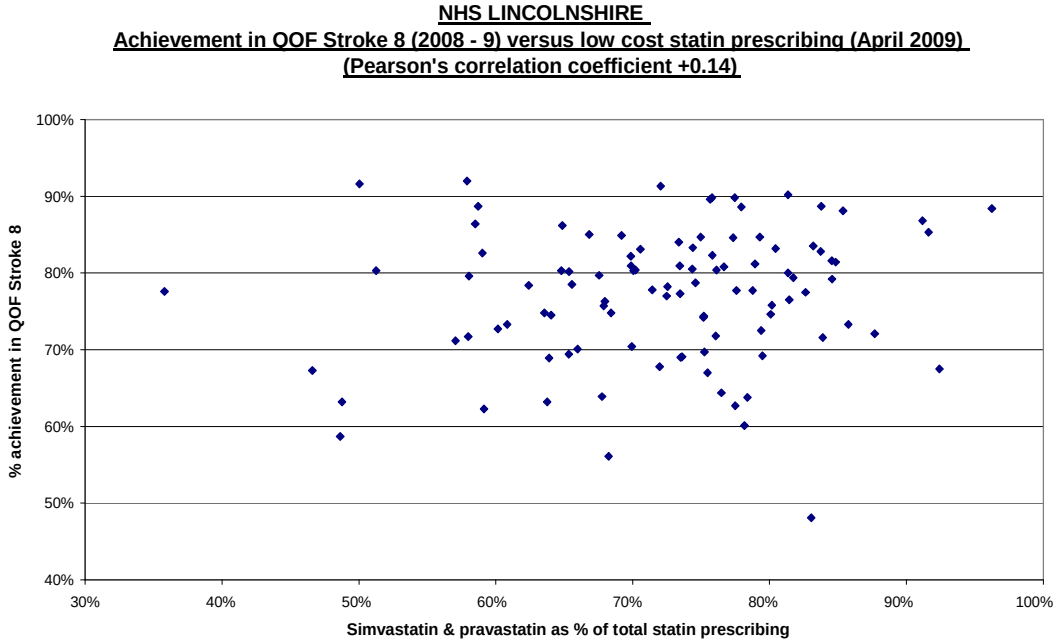
This simple analysis compared simvastatin and pravastatin as a percentage of total statin prescribing (equivalent to the Low Cost Statins (LCS) 'Better Care, Better Value' indicator) with practice performance against two Quality and Outcomes Framework (QOF) markers (CHD 8 and STROKE 8) in all practices in Somerset in 2006/07[1]. After exclusion of one outlier, the Pearson correlation coefficient (PCC) between low cost statin use and achievement of targets was statistically significant for both of the QOF markers, suggesting that there was some correlation between an increasing percentage LCS and decreasing practice performance against these two QOF indicators.

As the methodology was relatively simple to replicate, the New Trial Assessment Group undertook the same analysis using April 2009 percentage LCS figures for all Lincolnshire practices and QOF data for 2008/09. The CHD 8 and Stroke 8 scatter graphs are reproduced below:

CHD 8: The percentage of patients with CHD whose last measured total cholesterol (measured in the last 15 months) is 5 mmol/L or less (40 – 70%)



STROKE 8: The percentage of patients with stroke or TIA whose last measured total cholesterol (measured in the last 15 months) is 5 mmol/L or less (40 – 60%)



(Note: A Pearson correlation coefficient (PCC) of -1 indicates perfect inverse correlation between 2 variables. A value of 0 indicates no correlation)

PACEF Comment:

An exact repetition of the methodology of this study using recent Lincolnshire general practice data showed no correlation between CHD8 and LCS percentage (PCC +0.01) or Stroke 8 and LCS percentage (PCC +0.14). In addition, DM17 (percentage of patients with diabetes whose last measured total cholesterol (measured in the last 15 months) is 5mmol/L or less) was plotted against LCS percentage with a similar lack of correlation (PCC -0.03). Lincolnshire results correlate with a recent study published by Duncan Petty and colleagues that similarly found no evidence of a statistically significant association between the proportional use of low cost statins by PCTs and success in achieving the QOF national cholesterol targets in 2005/06 (CHD, stoke and diabetes)[2]. As a result of this, PACEF reject the contention of the Hickman paper and do not accept that high LCS percentage performance compromises practice performance against relevant QOF indicators.

References:
(1) Hickman J. Does higher usage of low-cost statins correlate with a poorer achievement in cholesterol quality markers for secondary prevention? *Br J Gen Practice* 2010; 60:50 – 52.
(2) Petty D et al. Can cheap generic statins achieve national cholesterol lowering targets? J Health Serv Res Policy 2008; 13: 99 – 102

MEDICINES AND HEALTHCARE PRODUCTS REGULATORY AGENCY: DRUG SAFETY UPDATE (JANUARY 2010)

Phenytoin: risk of Stevens-Johnson syndrome (SJS) associated with *HLA-B*1502* allele in people of Thai or Han Chinese ethnic origin

- Presence of the *HLA-B*1502* allele in people of Thai or Han Chinese ethnic origin may be associated with an increased risk of SJS with phenytoin.

- Phenytoin should be avoided in *HLA-B*1502* – positive individuals wherever possible. Use of phenytoin should only be considered where the benefits are thought to outweigh the risks.
- SJS is a life-threatening antiepileptic-related cutaneous reaction.
- The prevalence of *HLA-B*1502* is 8.2 to 9% in the Thai population and 8.6% in the Han Chinese population. Prevalence is extremely low in the Caucasian population (1-2%).

Methylphenidate: new patient information

- Treatment with methylphenidate should be supervised by a specialist in childhood or adolescent behavioural disorders.
- Diagnosis should be made according to DSM-IV criteria or ICD-10 guidelines. It should be based on a complete history and evaluation and not solely on the presence of one or more symptoms.
- Children and adolescents should have rigorous pre-treatment screening (i.e. complete history, relevant examination including psychiatric disorders or symptoms, cardiovascular status, height and weight).
- Patients should be monitored regularly during methylphenidate treatment including: BP and pulse, height, weight, appetite, onset or worsening of psychiatric symptoms and symptoms suggestive of heart disease.
- Treatment should be reviewed annually to determine whether continuation is needed.

PACEF Comment:
Shared care guidelines for treatments for attention deficit hyperactivity disorder (ADHD) are currently under review and will incorporate MHRA recommendations in future versions.

Acknowlegements

Many thanks to Cathy Johnson, Interface Lead Pharmacist, NHSL and Gill Kaylor, Prescribing Adviser, NHSL for their contributions to this edition of the *PACE Bulletin*.

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