

## Interaction between clopidogrel and PPIs

Concomitant use of a proton pump inhibitor (PPI) with clopidogrel should be avoided unless considered essential. This is due to concerns that PPIs may reduce the effectiveness of clopidogrel. Product information for all clopidogrel-containing medicines is being amended to reflect this.<sup>1</sup>

### Action

In the UK, the MHRA has issued the following advice:<sup>2</sup>

- The need for PPI therapy in patients who are also taking clopidogrel should be reviewed at their next appointment: avoid concomitant use of these medicines unless considered essential
- Prescribe PPIs in line with their licensed indications, where possible
- Check whether patients who are taking clopidogrel are buying over-the-counter omeprazole and consider whether another gastrointestinal (GI) therapy would be more suitable.

This new advice presents a good opportunity to review people on clopidogrel and a PPI. Healthcare professionals should consider stopping either the clopidogrel if it is being used outside NICE guidance (see below) or beyond the recommended period, or stopping the PPI, or stopping both, unless considered essential. If the original reason for using clopidogrel was due to GI intolerance on aspirin alone, switching to aspirin plus a PPI would seem a reasonable approach. For patients who need to continue taking clopidogrel and also require gastroprotection, there is currently insufficient evidence to recommend H2-receptor antagonists (H2RAs) or other GI therapies as alternatives to PPIs.

### What is the background to this?

Clopidogrel can cause GI symptoms and is, therefore, frequently prescribed with a PPI. The EMEA's Committee for Medicinal products for Human Use (CHMP) has concluded that, when clopidogrel and a PPI are taken together, mainly observational studies suggest that a significant interaction might occur. This could make clopidogrel less effective and result in patients being at an increased risk of thrombotic events, including myocardial infarction (MI). One possible explanation for this observation is that some PPIs prevent the conversion of clopidogrel into its biologically active form in the body, thereby reducing its effectiveness.

The US Food and Drug Administration (FDA) has also recently updated information about the ongoing safety review of clopidogrel, which we discussed in *MeReC Stop Press Blog No. 271*.

Neither the EMEA statement nor the FDA information makes reference to any individual PPI being any more or less likely to interact with clopidogrel than any other. The outcome studies do not fully reflect the pharmacokinetics of PPIs, and so more evidence is required before any specific recommendations can be made on the risk associated with individual PPIs. On the basis of pharmacokinetic data, other GI therapies (e.g. H2RAs, antacids) would not be expected to interact with clopidogrel. However, there are currently no substantial data from clinical outcome studies to support this.

The CHMP has recommended that the product information for all clopidogrel-containing medicines should be amended to discourage concomitant use of PPI and clopidogrel-containing medicines unless absolutely necessary.

### What does NICE say?

NICE guidance on the use of clopidogrel in non-ST elevation acute coronary syndrome (ACS) recommends clopidogrel, in combination with low-dose aspirin, in patients who have non-ST elevation ACS who are at moderate to high risk of MI or death. The guidance defines this group on the basis of clinical signs and symptoms with ECG changes and/or raised cardiac markers.

NICE guidance on clopidogrel and modified-release dipyridamole in the prevention of occlusive vascular events, which applies to patients who have had an occlusive vascular event or have symptomatic peripheral arterial disease, recommends clopidogrel alone only for those who are intolerant of low-dose aspirin. Aspirin intolerance is defined as proven hypersensitivity to aspirin-containing medicines or a history of severe dyspepsia induced by low-dose aspirin.

For more details see *MeReC Stop Press Blog Nos. 354 and 372*. Further information on the use of clopidogrel is available on the cardiovascular floors of NPCi.

### References

1. EMEA. Public statement on possible interaction between clopidogrel and proton pump inhibitors. 29 May 2009
2. MHRA. Drug Safety Update 2009;2(12):2-3

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## Intensive glucose control in type 2 diabetes

A meta-analysis of randomised controlled trials (RCTs)<sup>1</sup> suggests a small benefit of intensive glucose control in people with type 2 diabetes in reducing coronary heart disease (CHD), but not stroke or death. However, the benefit is not as great as that achieved by blood pressure (BP) control or lipid lowering. It remains uncertain whether intensive glucose control (e.g. the addition of hypoglycaemic drugs to reduce HbA1c to levels significantly below that often achieved in clinical practice) offers any significant benefit beyond that achievable by implementing other interventions to reduce cardiovascular (CV) risk (i.e. smoking cessation, exercise, losing weight, controlling BP, lowering cholesterol, taking metformin).

### What does this study claim?

There has been considerable debate over recent years on the importance of intensive glycaemic control relative to other measures for reducing CV risk in people with type 2 diabetes. The authors of this paper conducted a meta-analysis (MA) of five RCTs (total n=33,040) and found that intensive therapy statistically significantly reduced non-fatal MI (odds ratio [OR] 0.83, 95% confidence interval [CI] 0.75 to 0.93) and CHD (fatal and non-fatal MI; OR 0.85, 95%CI 0.77 to 0.93), compared with standard treatment. The number needed to treat (NNT) over five years was estimated as 87 and 69, respectively. However, there were no statistically significant differences between treatment groups with regard to stroke (OR 0.93, 95%CI 0.81 to 1.06) or all-cause mortality (OR 1.02, 95%CI 0.87 to 1.19). Intensive glucose control was associated with an **increased** incidence of hypoglycaemic episodes (38.1% vs. 28.6%) and severe hypoglycaemic events (2.3% vs. 1.2%). The mean reduction in HbA1c was 0.9% (approximately 10 mmol/mol) lower with intensive treatment rather than standard treatment (see *MeReC Stop Press Blog No. 356* for details on new reporting of HbA1c).

### So what?

We have consistently pointed out in other *MeReC Blogs* and NPCi materials on type 2 diabetes the need to consider glycaemic control alongside other important interventions (both lifestyle and drug interventions) to reduce CV risk. A recent *MeReC Stop Press Blog* points out the conflicting nature of evidence from RCTs on the benefits and risks of intensive glucose control. Large RCTs, such as ACCORD,

ADVANCE and VADT, all of which were included in the present MA, have not identified consistently a significant benefit of intensive glycaemic control in the treatment of type 2 diabetes with regard to CV outcomes and mortality (see *MeReC Rapid Review Blog Nos. 258, 147 and 64* for more details). Indeed, the ACCORD study was stopped early because of an **increased** risk of death in the intensive treatment arm.

This MA suggests that intensive glycaemic control may have a small benefit in reducing the risk of CHD, but no significant effect on reducing stroke or all-cause mortality. Furthermore, concerns have been raised about the methodology of the MA and its findings may not be generalisable to clinical practice (see *MeReC Rapid Review Blog No. 351* for details).

Intensive glycaemic control can be considered, where necessary, in addition to other interventions for reducing CV risk, but any potential benefits need to be considered against the increased risk of hypoglycaemia and drug-specific adverse effects. For example, glitazones increase the risk of heart failure, double the risk of bone fracture in women and there is some evidence to suggest that rosiglitazone, in particular, may be associated with an increased risk of MI. More information can be found on the type 2 diabetes floor of NPCi.

#### References

1. Ray KK, et al. Effect of intensive control of glucose on cardiovascular outcomes and death in patients with diabetes mellitus: a meta-analysis of randomised controlled trials. *Lancet* 2009;373:1765-72

## NICE updates guidance on management of type 2 diabetes

NICE clinical guideline (CG87)<sup>1</sup> partially updates recommendations for the management of type 2 diabetes, with new recommendations about blood glucose control with sitagliptin ▼, vildagliptin ▼, pioglitazone ▼, rosiglitazone, exenatide ▼ and insulin therapy. This updates and replaces CG66.

### What has changed?

Most of CG66 remains unchanged. Only the sections on the use of newer drugs to control blood glucose (sitagliptin ▼, vildagliptin ▼, pioglitazone ▼, rosiglitazone, exenatide ▼) and insulin therapy have new recommendations. There are no recommendations on liraglutide ▼ as this had not received marketing authorisation during the development of the guideline.

The new recommendations advocate the same level of HbA1c for the addition of extra glucose-lowering drugs as defined in the earlier guideline. That is a value of  $\geq 6.5\%$  (48 mmol/mol), or other higher level agreed with the individual, for people on one glucose-lowering drug and  $\geq 7.5\%$  (59 mmol/mol), or other higher level agreed with the individual,

for people on two or more glucose-lowering drugs or insulin. However, as we continue to say, the role of tight glycaemic control remains controversial (see previous article) and clinicians should focus on interventions to reduce CV risk in people with type 2 diabetes (e.g. smoking cessation, lowering blood pressure, lowering cholesterol).

The new recommendations are discussed in more detail in *MeReC Stop Press Blog No. 355* and the quick reference guide contains a helpful updated algorithm for blood-glucose lowering therapy.

#### References

1. NICE. Clinical guideline 87. Type 2 diabetes – the management of type 2 diabetes (partial update of CG66). May 2009

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