

NICE HTA: Clopidogrel and Modified Release Dipyridamole for the prevention of occlusive vascular events (review of TA No.90)



Joint Submission Diabetes UK and Association of British Clinical Diabetologists

October 2009

Diabetes UK

Diabetes UK is one of Europe's largest patient organisations. Our mission is to improve the lives of people with diabetes and to work towards a future without diabetes through care, research and campaigning. With a membership of 170,000, including around 6,000 health care professionals, Diabetes UK is an active and representative voice of people living with diabetes in the UK.

ABCD

The Association of British Clinical Diabetologists is the national organisation of Consultant Physicians in Britain who specialise in Diabetes Mellitus. Most are also Acute General Physicians, and many are also Specialists in Endocrinology and Lipid Metabolism. ABCD was established in 1997 with the principal objective of ensuring high quality care for all UK diabetes patients. It is essentially a professional organisation committed to the preservation and support of diabetes specialist care services. ABCD believes that local diabetes specialists are uniquely qualified to provide guidance and leadership for district diabetes services.

Facts about diabetes

- Prevalence of diabetes is more than 2.6 million in the UK.¹
- Diabetes affects the young and old, and has particularly poor outcomes in those of lower socio-economic status and in those from black and minority ethnic groups.^{2,3}
- Evidence is available supporting the need for improved education of people with diabetes and their carers if better control and improved outcomes are to be achieved.^{4,5,6}
- Diabetes, if undetected or not well managed, can lead to many complications and have a devastating impact on quality of life.

Declaration

Diabetes UK received no more than 3.6 per cent of income from pharmaceutical companies in 2008. Bristol Myers Squibb, Sanofi Aventis and Boehringer Ingelheim either have or will be providing income in the coming year.

Executive Summary

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- People with diabetes have an increased risk of cardiovascular disease. They are also considered a high risk population as once they have established CVD they have an increased risk of further occlusive vascular events, and are seen to have a prothrombotic status, with more diffuse and aggressive atherosclerosis.
- Therefore it is very important people with diabetes have access to safe and effective treatments to reduce their risk of further occlusive vascular events. An individually tailored approach to the use of these preventative treatments should be taken. Clopidogrel and modified release Dipyridamole, as well as aspirin, should be available as antiplatelet therapies to enable clinicians and people with diabetes a range of treatments to choose from.
- Individually tailored decisions about the most suitable antiplatelet therapy should be made by the healthcare professional in partnership with the person with diabetes and should take into consideration the following factors:
 - Licensed indications of the treatment
 - Clinical suitability, efficacy and patient choice
 - Quality of life considerations including known side effects such as headaches, bleeding, gastritis, nausea, vomiting
 - Frequency of medication administration
 - Risks, safety, and contraindications

Detailed Response

Background and access to antiplatelet technologies for secondary prevention

People with diabetes have an increased risk of developing cardiovascular disease and it is considered one of the long term and life threatening complications of diabetes.¹ This is due in part to prolonged high blood glucose levels that are not within what is considered a normal glycaemic range. This can result in blockages to vessels thereby increasing the risk of cardiovascular disease. In addition people with diabetes also need to manage further risk factors such as blood pressure and blood lipid levels as these are also associated with the development of long term complications including cardiovascular disease.

The cardiovascular risk in people with diabetes is the same as people without diabetes who have had a previous heart attack.¹ Cardiovascular disease accounts for 44 per cent of fatalities in people with Type 1 diabetes and 52 per cent in people with Type 2 diabetes.¹ Furthermore, women with Type 2 diabetes are at 50 per cent increased risk of death from CHD compared to men, and people with Type 2 diabetes overall have a two fold increased risk of stroke in the first five years of diagnosis compared to the general population.¹

The evidence base highlights people with diabetes as a high risk population for occlusive vascular events, as they are considered to have a “pro thrombotic status”⁷ and have a “more diffuse and aggressive nature of atherosclerosis.”^{7,8}

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Taking these factors into account it is clearly essential that people with diabetes have access to a range of antiplatelet therapies, so that treatment can be tailored to a person's individual clinical need and the suitability of treatment options. Without access to effective antiplatelet therapy people with diabetes will be at even greater risk of having further vascular events or mortality as a result of these events.

Patient Choice

Patient choice, control, and personalised care are key elements of health policy for people with long term conditions.⁹ Decisions about which antiplatelet therapy is chosen must not be made on the grounds of cost effectiveness alone. People with diabetes should be supported to make a decision in partnership with their healthcare professional regarding the choice of antiplatelet therapy. People with diabetes will need access to high quality, objective, information about the different treatment agents to inform the decision making process. The decision making process is likely to include consideration of the following factors:

- Licensed indications of the treatment
- Clinical suitability, efficacy and patient choice
- Quality of life considerations including known side effects such as headaches, bleeding, gastritis, nausea, vomiting
- Frequency of medication administration
- Risks, safety, and contraindications

Therefore information about these factors should be available to people with diabetes. In a consultation event with people with diabetes, choice of treatment options and information about treatments to support the decision making process were emphasised as key areas of patient choice.¹⁰

Clinical efficacy

Clopidogrel

The CAPRIE study demonstrated the clinical efficacy of Clopidogrel in comparison to aspirin for high risk populations, including people with diabetes, and even more so for people with diabetes treated with insulin.^{11,12} The use of Clopidogrel in people with diabetes treated with insulin prevented 38 more events per 1000 in this population compared to aspirin. In people with diabetes overall, Clopidogrel prevented 21 more events per 1000 compared to aspirin.¹¹ Further analysis of the CAPRIE participants found a reduced rate of re-hospitalisation for ischaemic events in people treated with Clopidogrel.¹¹ Analysis demonstrated the cost effectiveness of the use of Clopidogrel to prevent further atherothrombotic disease, particularly in high risk groups including people with diabetes.¹² The side effect profile of Clopidogrel was seen to be "at least as good"¹² as aspirin when these therapies are used separately.¹²

Modified Release Dipyridamole

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The ESPS-2 and ESPRIT studies have demonstrated the increased benefit of modified release Dipyridamole in combination with aspirin, compared to the use of aspirin alone to prevent TIA and stroke.^{13,14,15} In the ESPS-2 study the combination of modified release Dipyridamole and aspirin, reduced stroke recurrence by 23 per cent compared to aspirin as monotherapy. Dipyridamole in combination with aspirin was associated with less bleeding than aspirin alone although this finding was not significant. The combination of therapies was found to have a similar frequency of bleeding events compared to aspirin alone.¹⁵ However this dual therapy did not convey advantage over aspirin in preventing “total death, vascular death or myocardial infarction,” but it also “did not increase the incidence of MI.”¹³

Side effects

Clopidogrel

Gastro intestinal effects

Vomiting and diarrhoea have been identified as either common or uncommon side effects of Clopidogrel. As these symptoms can affect blood glucose levels because of the malabsorption of food it is important to make people with diabetes aware of these effects.

Modified Release Dipyridamole

Headaches

Headaches are cited as an undesirable effect of this treatment on the SPC. This was also identified in the trials of Dipyridamole, with the ESPRIT trial citing 26 per cent of people discontinuing with the trial identifying headache as one of the reasons for this.¹⁴

Dizziness and Sweating

The SPC identifies that Modified Release Dipyridamole can cause sweating and dizziness. People with diabetes should be made aware of these side effects as they are also symptoms of hypoglycaemia for some people with diabetes.

Gastro intestinal effects

Vomiting and diarrhoea have been identified as side effects of Modified Release Dipyridamole. As these symptoms can affect blood glucose levels because of the malabsorption of food it is important to make people with diabetes aware of these effects.

Health related contraindications and Risks

People with diabetes and nephropathy, renal impairment

The SPC for Clopidogrel carries a warning with regard to individuals with renal impairment. As people with diabetes are at increased risk of nephropathy (kidney disease) it is important that they are screened for kidney function and creatinine clearance to inform the decision making process with regards to this treatment option.

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A post hoc analysis of the use of Clopidogrel in combination with aspirin in people with diabetes and nephropathy identified that this group of individuals would be at increased risk of cardiovascular and overall mortality when Clopidogrel is used in combination with aspirin, compared to aspirin alone.¹⁶ This is an important consideration in the decision making process regarding antiplatelet therapy for people with diabetes and nephropathy, and people with diabetes should be screened for nephropathy to inform the decision making process.

Combination therapy of Clopidogrel and aspirin

The MATCH and CHARISMA studies both identified the increased risk of combining Clopidogrel with aspirin in people from high risk groups, including people with diabetes. These studies demonstrated an increased risk of bleeding when the therapies are used in combination.¹⁵ The use of the agents in combination compared to aspirin alone also did not appear to convey additional benefit in reducing the rate of MI, stroke or death from cardiovascular causes in people with multiple risk factors or existing cardiovascular disease.¹⁵ A different study however demonstrated the benefit of this combination therapy in reducing one year mortality in survivors following STEMI, where treated with early reperfusion therapy.¹⁷

This increased risk of bleeding will need to be considered by a healthcare professional and person with diabetes when making decisions about treatment options.

Bleeding including intraocular bleeding

The SPC identifies that conjunctival, ocular and retinal bleeding are all uncommon but possible side effects of Clopidogrel and it should be used with caution in people at increased risk of bleeding. People with diabetes are at increased risk of microvascular complications, including retinopathy (damage to the seeing part at the back of the eye). Therefore it is important that this is appropriately assessed in considering Clopidogrel as a treatment option.

Clopidogrel and Proton Pump Inhibitors

The MHRA have recently issued an alert identifying that people taking Clopidogrel and Proton Pump Inhibitors should not take the PPI unless absolutely necessary as it reduces the effect of Clopidogrel.¹⁸ As PPI's can be taken to relieve gastritis which is a side effect of Clopidogrel this must be taken into consideration with regard to quality of life implications.

Hypotensive effects of Dipyridamole

The hypotensive effects of Dipyridamole have been noted in the SPC, including enhancing the hypotensive effects of blood pressure lowering medications. Many people with diabetes may be taking blood pressure lowering medications, as blood pressure is one of the key biomedical markers to be controlled in diabetes management. People with diabetes are at risk of autonomic neuropathy and hypotension as a result of this therefore it is important to screen for this condition and ensure the person with diabetes is informed of these effects, to inform the decision making process.

Dipyridamole - MI, severe Coronary Artery Disease, Unstable Angina, left ventricular outflow obstruction and haemodynamic instability

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The SPC recommends that Modified Dipyridamole is used with caution in people with any of the conditions above. Furthermore it may worsen the symptoms of CHD, such as angina or arrhythmias and cause tachycardia. CVD is a long term complication of diabetes and people with diabetes are at increased risk of CVD. Therefore the existence of these conditions in the person's medical history and current status must be established to inform the decision making process.

Conclusion

Diabetes UK recommends these technologies are available as antiplatelet therapies provided they are considered safe and effective. Decisions about treatment choice should be individually tailored and made in partnership between the healthcare professional and person with diabetes. In considering the treatment options available the following factors should inform decision making:

- Licensed indications of the treatment
- Clinical suitability, efficacy and patient choice
- Quality of life considerations including known side effects such as headaches, bleeding, gastritis, nausea, vomiting
- Frequency of medication administration
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