Which oral agent to use when metformin is no longer effective?

The history of the biguanide metformin is interesting. Although first synthesised over ninety years ago and known to have glucose lowering properties, its potential as a therapeutic agent in the treatment of diabetes was either ignored or forgotten about until the 1970s. It has now become perhaps the most widely prescribed oral anti-diabetic drug worldwide. It is easy to appreciate the reasons for its popularity. It is relatively cheap and has a proven effectiveness in improving glycaemic control in patients with type 2 diabetes (T2DM). It has, in addition, desirable cardiovascular protective properties and can enable prevention of weight gain. The drug has a reasonable safety profile as it has a low risk of causing significant hypoglycaemia; the more commonly described adverse effects are gastro-intestinal (described as being mild and short lived although many patients would dispute this) and a tendency to cause lactic acidosis in well described circumstances which admittedly are rare and preventable. In many respects therefore, metformin is almost an ideal therapeutic agent.Sadly, the experience of both patients and clinicians is that following an initial period of improved glycaemic control, it slowly fails to be effective when used on its own. The next step for many T2DM patients is to combine the use of metformin with insulin or another oral anti-diabetic agent. The review by Vella et al., considers the additional and alternative oral anti-diabetic therapeutic options that are currently available. Several families of anti-diabetic drugs are appraised in terms of known mode of action, effectiveness and safety. The sulphonylureas have the advantage of familiarity and low cost but are associated with hypoglycaemia and weight gain. The so-called glititins represent a newer class of oral hypoglycaemic agent which appear to have a neutral effect on weight and an acceptable safety profile; however their cardiovascular effects are as yet uncertain. The glitazones have been shown to effectively reduce insulin resistance but some drugs in this category have been withdrawn because of an apparent increased risk of adverse cardiovascular events. Glucagon-like peptide (GLP-1) agonists represent a newer class of anti-diabetic agent that increases insulin secretion in response to food and which have a low risk for weight gain and hypoglycaemia. The authors conclude that at present metformin represents the best available drug for first line treatment of T2DM but none of the other available agents can be considered as a preferred option for second line “add-in” treatment.

Timing of percutaneous coronary intervention in patients with non ST elevation acute coronary syndrome.

Navarese et al consider the emergency management of non ST elevation acute coronary syndrome (NSTE-ACS). They acknowledge the proven improved outcomes in terms of both morbidity and mortality for NSTE-ACS patients who receive percutaneous coronary intervention (PCI) when compared with those who are treated more conservatively. The question then to be answered relates to the most appropriate timing for PCI. Five randomised control trials describing the clinical course of over 4,000 NSTE-ACS patients were analysed. End points included all cause mortality, myocardial infarction (MI), coronary revascularizations and 30-day major bleeding complications. It was concluded that early invasive intervention does not appear to significantly improve clinical outcomes when compared to a more delayed approach; furthermore there was no significant reduction in major bleeding complications for those patients treated by means of the early invasive approach. While earlier intervention could have the benefit of prompt definitive diagnosis and ultimately an earlier discharge, a delayed strategy might offer other benefits as a result of plaque passivation by optimal medical treatment followed
by intervention on more stable plaques. In conclusion, it is argued that routine early invasive strategy in patients with NSTE-ACS is not always warranted.

**Definition of acute kidney injury: the need for more precision**

The term acute kidney injury (AKI) is often used and refers to a sudden deterioration in renal function. AKI is relatively common in ill hospital in-patients and has serious implications for their clinical management. It seems obvious that early diagnosis should facilitate the institution of appropriate therapeutic measures. However what does AKI mean? Obviously any definition would refer to abnormal creatinine levels and falling urinary output. For a definition of any clinical disorder to be useful it must have consensus acceptance amongst clinicians and demonstrate consistency when applied to clinical situations. Ostermann describes the evolution of an agreed set of diagnostic AKI criteria beginning in 2001, the RIFLE classification in 2004 and the more recent Acute Kidney Injury Network (AKIN) classification. The authors then applied the 3 most recent AKI definitions to the clinical management of over 40,000 and compared their performance. They found good correlation between the diagnostic methods with respect to definition of disease severity and outcome but disappointingly, all three methods were found to be at risk of not identifying patients with progressive deterioration of renal function. Hence, while the benefits of currently agreed AKI diagnostic criteria are acknowledged they should not be the only means used for assessment of patients at risk of this disorder.

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