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EDITORIALS

Pharmacotherapy for type 2 diabetes in very elderly patients: practicing nihilism or pragmatism?

For a multitude of reasons—whether rightly or wrongly—very elderly people are often excluded from drug trials. In the era of evidence-based medicine, this means that if a patient was already on some medication when they became 'elderly', prescribers have some options—to continue to prescribe the drugs that they had been on, in the hope that the evidence derived from studies on younger patients still holds true or, as 'purists', stop any medication for which there is no evidence in this age group. Anecdotally, I would suggest the former happens more frequently than the latter. But what of those people who were first diagnosed after they were 80 years old? In this age group, where almost no drug trails have been done, do the same principles hold true? Where no evidence exists for pharmacological intervention, should evidence from younger patients be extrapolated to justify initiating treatment in very elderly subjects? In type 2 diabetes, there are very few data looking at outcomes in elderly patients with aggressive glycaemic, blood pressure and lipid control, despite the high prevalence of the condition in this age group.

The authors of the accompanying study have used the well-established Clinical Practice Research Datalink to assess prescribing habits for type 2 diabetes in the very elderly over time. These authors showed that between 1990 and 2013, 26,230 people were diagnosed as having new onset type 2 diabetes over the age of 80. They showed that 51% of these cases were given no oral hypoglycaemic agents at all. That still means that almost half were given medication in a non-evidence-based fashion.

To try to determine why prescribing patterns vary will need some further analysis—were those who were not prescribed any glucose-lowering agents an older age group, did they have more co-morbidities and were there any other differences between those given medication for their diabetes and those who were not? Was the lack of prescribing a 'purist' approach? Unfortunately, the database does not allow these questions to be answered.

Glycaemic control and blood pressure control

Since 1990, there have been several major cardiovascular outcome trials in diabetes. Starting with the United Kingdom Prospective Diabetes Study (UKPDS) which compared the effects of tight glycaemic control and tight blood pressure on the risk of developing micro and macrovascular complications with the 'standard of care' [1, 2]. This seminal study showed that aggressive treatment led to a reduction in the risk of developing complications, but that macrovascular outcomes only started to show a difference in the glycaemic control arm 5 years after the intervention started, while aggressive blood pressure control made a difference almost immediately. Partly as a result of the UKPDS, the current guidelines for the management of type 2 diabetes have evolved to recommend that metformin be used early after the diagnosis has been made [3]. This may account for why metformin prescribing increased so substantially over time, despite the increased likelihood of renal impairment and cardiac failure in this age group. In addition, the rapidly decreasing use of sulfonylureas may reflect the increasing evidence to show that they are associated with severe hypoglycaemia and cardiovascular death [4, 5]. With respect to blood pressure, the Hypertension in the Very Elderly Trial (HYVET) study may also account for the increase in antihypertensive prescribing [6]. That study of 3,845 patients (6.9% of whom had diabetes) looked specifically at treating hypertension in the over 80 year olds and showed that targeting a blood pressure of 150/80 mmHg for a median of 2 years was associated with significant reductions in heart failure, deaths from stroke and all-cause mortality, with strong trends towards reducing death from CVD.

The authors of the accompanying study show that the average life expectancy of the entire cohort was quite short—a mean of 3.4 years. Thus, if life expectancy is relatively short, the question arises: why aggressively treat someone with a number of different oral hypoglycaemic agents (from which they may suffer side effects) when they may not live long enough to see the benefits—as opposed to the antihypertensives, where the benefits were seen early.

The American Diabetes Association have advocated an approach dependent on the relative health status of an individual, with tighter glycaemic and blood pressure targets set for those who have the longest life expectancy [7].

Along with this, we must consider the inappropriate use of drugs—or, more accurately, the appropriate omission of drugs. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) study showed that aggressive glucose lowering was associated with increased morbidity, often in the form of hypoglycaemic episodes [8]. That study randomised over 10,000

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patients with a mean age of 62 years to a glycated haemoglobin (HbA1c) target of either below 6.0% (42 mmol/mol) or 7.0–7.9% (53–64 mmol/mol). After 1 year, they achieved HbA1c levels of 6.4% (47 mmol/mol) and 7.5% (58 mmol/mol) in each group, respectively, but the rates of severe hypoglycaemia were significantly higher and the mortality in the intensive arm was 22% greater than the standard treatment arm [8]. The study was stopped prematurely due to these results. It may also be that the ACCORD study and others that showed no macrovascular or mortality benefit from aggressive glycaemic control but significantly higher levels of severe hypoglycaemia [9, 10] were part of the reason that prescribing of oral hypoglycaemic agents decreased to only 39% of people with newly diagnosed type 2 diabetes in 2010–13, after reaching a peak of 60% in 1997–99. Clearly more work is needed to try to explain these results.

Lipids

The original study showing the benefits of lipid lowering was published in 1994 [11]. Since then, a host of other trials have all shown that aggressive lipid lowering is beneficial in high-risk populations. As a result lipid-lowering agents—statins usually—are now advocated for primary prevention in patients with type 2 diabetes who have a 10% or greater 10-year risk of developing cardiovascular disease (CVD) using the QRISK2 assessment tool [12]. However, the mean age for the studies looking at primary prevention of CVD in people with type 2 diabetes was 63.8 years (SD 8.4) [13]. The National Institute for Clinical and Healthcare Excellence (NICE) acknowledges that 'few trials assessing cardiovascular outcomes have recruited many people older than 80 years yet the important effect of age on CVD risk suggests that all people in this group should be offered statin therapy'. They go on to say that 'there is no evidence to validate the CVD benefits and side effects of statin therapy such as effect on muscle and renal function in this age group' [12]. So, even in this era of evidence-based medicine, NICE advocates a non-evidence-based approach.

Antiplatelet agents

The use of antiplatelet agents, in particular aspirin, has been hotly debated since the mid-2000s, with their use as part of multiple risk factor intervention showing cardiovascular benefit [14], although aspirin use is also associated with increased risk of intracerebral and gastrointestinal haemorrhage. Aspirin is currently not licensed for use in primary prevention of CVD. However, the current recommendations from NICE suggest that aspirin be given to those over 50 years old when the blood pressure is <145/90 mmHg [15]. The American Diabetes Association recommendation is in line with their statin advice, that in those with a 10% or greater 10-year risk of developing CVD, aspirin should be considered in primary prevention [16]. The results of the A Study of Cardiovascular Events in Diabetes (ASCEND) study are eagerly awaited to answer the question of whether aspirin use is beneficial; however, this will again largely be in a different age group and the same issue about extrapolation will arise.

In summary, these descriptive data need to be interpreted in parallel to the results of contemporaneously published cardiovascular outcome studies. As the evidence base has evolved, so prescribing habits have changed. As newer agents and new classes of drug become available, prescribing habits are likely to change again. Until very elderly patients are routinely included in drug trails, we will have to continue to use our clinical judgement about what is best for the individual patient in front of us. We still have a long way to go before we know what drugs to safely use in very elderly patients.

Key points

- Despite the lack of evidence for doing so, almost half of patients diagnosed with new onset type 2 diabetes over the age of 80 years are prescribed oral hypoglycaemic agents.
- Prescribing patterns for these patients over the last 25 years reflect the contemporaneous results of large cardiovascular outcome studies conducted in younger cohorts.
- There remains active debate whether the results from these outcome trials can be extrapolated to very old subjects or whether, where there is no clear evidence of benefit, prescribing should be avoided.

Conflicts of interest

The author is an employee of the UK National Health Service.

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Exercise regimens, bone health and fracture prevention in later life: evidence still needed

The need to do everything possible to reduce fragility fractures in later life is agreed. By far the largest research investment and resulting evidence to date has targeted drugs to enhance bone mineral density (BMD), and the broad benefit/risk effectiveness of these agents in the primary and secondary prevention of fractures is established. There remain, nevertheless, some issues of treatment duration, medication compliance, relative cost-effectiveness and drug safety.

The potential contribution of non-pharmacological approaches is therefore important, and it is perhaps unsurprising that this is largely marginalised in the industry drug trial literature. There is, nevertheless, a growing body of evidence. Most importantly, falls incidence can be reduced by interventions that include defined exercise regimens either alone or as part of a multifactorial approach (depending on the population group and individual assessment), although the proportional contribution of falls reduction to fracture prevention has yet to be definitively quantified.

A related question is whether BMD might be conserved or enhanced by exercise regimens. There is broad generic, age-independent evidence for a positive effect of weight bearing and mechanical loading on bone mass and mineralisation, but remaining unclarity on the efficacy of exercise interventions targeting this amongst older people—for whom? when? exactly how? and for how long? Although other measures of structural bone strength (v. mineralisation) are recognised, BMD looks set to remain the broad pragmatic indicator of risk/benefit for the foreseeable future.

The available literature suggests a small potential benefit, but it has been heterogeneous in terms of (i) defining the exercise intervention and outcome measurement, (ii) BMD sites affected, (iii) duration of intervention and follow-up and (iv) population groups (although most studies have focused on relatively small samples of healthy community-dwelling older women) [1]. The study by Duckham *et al.* [2] published in the current issue comprises one of the larger subject samples to date (319) and investigates the effects of two commonly deployed falls prevention exercise regimens (the Otago Exercise and Falls Management Exercise Programmes—OEP & FaME) on BMD over 6 months, as part of a wider programme studying their influence on sustainable healthy physical activity in men and women over 65 recruited from primary care [3]. The finding of no beneficial effect on BMD in this 'real world' model is important and is relevant to commissioning in the immediate UK NHS context.

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