Antidiabetic pharmacotherapy for better cardiovascular health

Although several new drugs have become available for the treatment of type 2 diabetes, metformin – a drug used as the primary medication for decades – remains important as an antidiabetic medication. In sufficient doses, metformin is highly effective, and there is evidence to suggest it can prevent cardiovascular events. Similar evidence is not yet available for the newer drugs.

The growing prevalence of diabetes is a key concern whenever the adequacy of health care resources is discussed. This usually means type 2 diabetes, even though type 1 diabetes is becoming rapidly more common.

Type 2 diabetes is, in fact, a condition doctors diagnose after ruling out type 1 diabetes and all other types of the disease for which a detailed diagnosis is available. For practical purposes, it is customary to refer to a spectrum of closely related conditions as type 2 diabetes.

Type 2 diabetes is so common today due to our sedentary lifestyles and our body’s almost unlimited ability to store excess energy from food. This puts our metabolic regulatory mechanism under incredible stress.

Even in a healthy person, the beta cells responsible for insulin production in the pancreas weigh less than one gram, and insulin secretion mechanisms are extremely complex and susceptible to disruption. Insulin resistance and excess glucose in the bloodstream put beta cells to the test, which they sometimes fail. The resulting cell failure represents a downward spiral, which no proven drug therapy can prevent.

Too great a focus on drug therapy for high blood glucose
Individually designed drug therapy remains in its infancy. Therapies designed to lower blood glucose have advanced at an astonishing pace in recent years. However, evidence on the effectiveness of antidiabetic medication, including insulin, in the prevention of cardiovascular disease (a major complication of diabetes) is inconclusive.

The progressive nature of diabetes, advances in drug therapies, and market forces have directed much attention in diabetes care to drug therapies that lower blood glucose levels, assigning secondary importance to lifestyle management and the treatment of dyslipidemia and high blood pressure.

Although hemoglobin A1c (HbA1c) is a generally accepted primary variable in clinical trials, intensive drug therapy intended to lower HbA1c levels appears to increase the occurrence of cardiovascular events.

Rosiglitazone has changed the drug regulatory authorities’ views on antidiabetic medications
Following the publication of the results of the UK Prospective Diabetes Study (UKPDS), a landmark trial, the interaction between antidiabetic medications and HbA1c seemed fairly straightforward: metformin provides protection from cardiovascular events regardless of the decrease in HbA1c, while a decrease in HbA1c is a good surrogate endpoint for sulfonylureas and insulin efficacy.

Rosiglitazone was the first of the new insulin sensitizers adopted for therapeutic use in Europe in 2000. In 2007, a meta analysis was published, indicating that rosiglitazone increased the risk of myocardial infarction by 43% and cardiovascular disease mortality by 64% (Niessen and Wolski 2007). This meta analysis and the ensuing investigations lead to the withdrawal of the product from the market in the European Union and to tight restrictions in the USA in 2010. However, the marketing authorisation for another insulin sensitiser, pioglitazone, remained in effect as it was considered neutral in terms of cardiac events.

These incidents radically changed the drug authorities’ views on antidiabetic medications and their development. The US Food and Drug Administration FDA set new terms for granting marketing authorisations, requiring compliance with consistent criteria in order to demonstrate cardiovascular safety. A decrease in HbA1c or a neutral or even favourable effect on the risk factors in cardiovascular disease were not considered sufficient indicators of pharmaceutical efficacy or safety.

This requirement for prognostic evidence led to a significant tightening of the marketing authorisation criteria for antidiabetic medications. Today, the new pharmaceutical safety legislation allows the authorities to set a Post-Authorisation Safety Study, or PASS, as a condition for marketing authorisation.

Re-assessment of rosiglitazone
The negative results published later on intensive HbA1c treatment were a cause of further confusion. Last summer, the FDA re-assessed rosiglitazone, eventually concluding that its use does not involve any extra risk of cardiovascular disease (Hiatt et al. 2013).

FDA’s change of heart is raising suspicions about whether there were any real grounds for withdrawing rosiglitazone from the market earlier. In 2010, the FDA placed the Thiazolidinedione Intervention with Vitamin D Evaluation TIDE trial on clinical hold. This trial was designed to compare the risk of heart disease in patients receiving rosiglitazone, pioglitazone, or a placebo. Because the trial was suspended, a definitive answer will never be available. Glitazones do have known adverse side affects such as weight gain, swelling, impaired bone mineral density and fractures, and increased risk of heart failure.

However, if one product is withdrawn from the market, while another drug in the same class remains available, strong evidence is required of the harm caused by the withdrawn product. But what constitutes sufficient evidence to warrant a product’s withdrawal from the market? For the authorities, this is a difficult situation: reacting quickly may limit access to effective and clinically proven therapy in favour of a less researched treatment, and reacting slowly may expose a large number of people to the harmful effects of a drug.

The surge in incretin drugs poses no threat to metformin
Despite the surge in new drugs, the tried and tested metformin has held onto its position. Metformin has for long been dismissed as an ineffective drug that causes stomach problems. Moreover, a similar drug called fenformin was known to have a propensity for lactic acidosis. However, in the mid-1990s it was discovered that based on an adequate daily dosage and when properly administered, metformin was a safe and effective drug. Once evidence had been obtained on the improved prognosis, which was lacking with respect to other drugs,
The risk of hypoglycemia associated with incretin mimetics and gliptins is low. In terms of weight gain, they have a neutral effect; incretin mimetics have known side-effects are minor and any side-effects affecting the digestive tract are generally transient. Effects, and so-called DPP-4 inhibitors or gliptins prolong the half-life of the endogenously released GLP-1. These are easy to use, the prognosis for cardiovascular diseases addresses hypertension and dyslipidemia.

But as research and development continued, new discoveries were made. Researchers found that food ingestion immediately triggers hormone secretion in the final segment of the small intestine. The purpose of these GLP-1 (glucagon-like peptide 1) hormones is to enhance energy metabolism. As a result, the secretion of insulin in the pancreas increases while the secretion of glucagon decreases, thereby balancing the rise in blood glucose occurring after a meal (the incretin effect). GLP-1 also sends a safety message to the brain. Although GLP-1 as such is very short-acting, GLP-1 analogues or incretin mimetics (exenatide, liraglutide and lixisenatide) enhance its effects, and so-called DPP-4 inhibitors or gliptins prolong the half-life of the endogenously released GLP-1. These are easy to use, the known side-effects are minor and any side-effects affecting the digestive tract are generally transient.

The risk of hypoglycemia associated with incretin mimetics and gliptins is low. In terms of weight gain, they have a neutral effect; incretin mimetics may even cause significant weight loss. Being new products, they are rather expensive. Gliptins have been readily accepted in Finland; in fact, they have become the first supplementary drug for metformin.

The results of initial trials forecasting the occurrence of cardiac events in patients being given saxagliptin or alogliptin have been recently published. They did not show any increase in myocardial infarctions or cardiovascular deaths, but patients treated with saxagliptin had a higher prevalence of heart failure requiring medical care as well as a higher risk of hypoglycemia. No evidence presented itself in support of the cardiac event prevention effect suggested at the clinical stage. In both trials, the baseline level of HbA1c was 8.0%, and the HbA1c decrease was 0.3 percentage points higher than in the placebo group. This is a relatively modest outcome.

Concerns have been expressed on several occasions about the suspected harmful effects on the pancreas and patients included in the trial are vigilantly monitored for pancreatitis and pancreatic cancer. The editorial in the Finnish Medical Journal (Yki-Järvinen 2013) opened a discussion on the effectiveness of the extensive use of this class of drugs. One of the lessons learned is that the modest HbA1c decrease achieved with these medications does not correlate to an improved cardiac disease prognosis.

Glucose disposal agents the latest novelty
Glucose disposal agents are oral antidiabetic medicines developed for the treatment of type 2 diabetes. They prevent renal glucose reabsorption. Drug-induced glycosuria results in a lower blood glucose and slight weight loss.

Like other oral antidiabetic medications, glucose disposal agents lower HbAc1 (Leinonen and Niskanen 2013). Although nothing in the clinical trial results points to a risk of cardiac disease, no outcome study results are currently available. It will be interesting to see how these drugs are positioned in the pharmaceuticals markets, and how effective and safe they are in clinical use.

Focus switching from sugar to fats and blood pressure
The blood glucose lowering antidiabetic drug therapy has changed a great deal in a short time, as has the price of therapy. In practice, the drug reimbursement system is the central mechanism used to target pharmaceutical care. Whether this is sensible is an entirely different matter.

The drugs used to treat diabetic hyperglycemia are in the highest reimbursement category, with the exception of products recently introduced to the market and GLP-1 analogues, whose reimbursement is limited. Treatment that will have a significant impact on the prognosis for cardiovascular diseases addresses hypertension and dyslipidemia.

The treatment of hyperglycemia addresses symptoms caused by changes in blood glucose levels and the risk of microvascular organ damage. And last but not least: lifestyle changes. These provide the best overall benefit as well as being dramatically effective in the prevention of type 2 diabetes. The significance of drug therapy grows as the disease progresses.

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