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LEADING ARTICLE

Balancing Benefits and Risks in Patients Receiving Incretin-Based Therapies: Focus on Cardiovascular and Pancreatic Side Effects

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Abstract Incretin-based therapies either increase endogenous levels of glucagon-like peptide-1 by prolonging its half-life (DPP-4 inhibitors) or directly stimulate its receptor (glucagon-like peptide-1 analogues; GLP-1 RA). They are currently widely used for the treatment of patients with type 2 diabetes mellitus owing to good antidiabetic efficacy, low risk of hypoglycemia, and relatively few other side effects. They also offer potential additional benefits such as weight neutrality or weight loss, positive effects on blood pressure and lipid levels, and potential cardio- and neuroprotectivity. Some experimental and clinical studies have raised concerns with respect to potential cardiovascular and pancreatic side effects of these therapies such as increased risk of heart failure with DPP-4 inhibitors as well as acute pancreatitis and pancreatic cancer with both classes. The available data are at present not robust enough to enable firm conclusions regarding these potential associations. Nevertheless, some recent data suggest a possibility of slightly increased risk of acute pancreatitis with GLP-1 RAs while they do not indicate increased risk of pancreatic cancer. Ongoing cardiovascular outcome trials will shed more light on the possible cardioprotective effects of incretin-based therapies as well as on the possible interconnection of DPP-4 inhibitors and heart failure.

Key Points

The prevalence of type 2 diabetes is increasing worldwide.

Incretin-based therapies improve diabetes compensation without risk of hypoglycemia.

Their cardiovascular and pancreatic safety still needs to be confirmed by further studies.

1 Introduction

Increasing prevalence of type 2 diabetes (T2DM) worldwide and its close interconnection with obesity, arterial hypertension, dyslipidemia, and other pathologies commonly referred to as metabolic or insulin resistance syndrome [1] makes T2DM one of the most significant therapeutic challenges of the twenty-first century [2]. Studies have shown that early diagnosis and effective treatment of T2DM and related co-morbidities are necessary to prevent chronic micro- and macrovascular complications [3, 4]. Although several classes of glucose-lowering drugs are available, more than half of T2DM patients do not reach optimal glucose control because of the progressive nature of T2DM, suboptimal compliance of patients to diet and lifestyle measures, as well as side effects of most antidiabetic drugs, in particular hypoglycemia and weight gain [5].

In recent years, the focus of novel antidiabetic drug development has shifted from the traditional glucocentric view towards a more complex approach emphasizing the importance of their beneficial effects on related co-

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morbidities and cardiovascular risk factors [6] and fewer side effects. Incretin-based therapies represent one of the results of this approach having not only good antidiabetic efficacy but also other positive non-glycemic effects [7, 8]. In this paper, we review possible cardiovascular and pancreatic side effects of incretin-based therapies and put them into overall perspective with their known benefits relative to other glucose-lowering drugs.

2 Incretin-Based Therapies

The incretins are peptide hormones released from the small intestine upon meal ingestion that stimulate insulin secretion from pancreatic β-cells and reduce excessive glucagon secretion from pancreatic α-cells thereby alleviating two important defects present in type 2 diabetes [9]. Of the two currently known incretins, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), only therapies based on the effects of GLP-1 are utilized in clinical practice [10]. The mode of action of the first class of incretin-based therapies referred to as gliptins or DPP-4 inhibitors is the inhibition of the enzyme dipeptidyl peptidase-4 (DPP-4) that breaks down circulating GLP-1 [11]. The treatment with DPP-4 inhibitors thus prolongs the half-life of endogenous GLP-1 increasing its concentrations to the high-normal physiological range [12]. The second class of incretin-based therapies relies on the stimulation of GLP-1 receptor with compounds resistant to DPP-4 degradation called GLP-1 receptor agonists or GLP-1 receptor mimetics [13]. The concentrations of active compounds are closer to the pharmacological range of GLP-1 being approx. 3- to 5-fold higher than endogenous GLP-1 levels [12]. Both DPP-4 inhibitors and GLP-1 RA effectively improve glucose control with very low risk of hypoglycemia, with GLP-1 RA having more gastrointestinal side effects but additional benefits of decreasing body weight and blood pressure [14]. Furthermore, cardioprotective, neuroprotective, and β-cell-protective effects of incretin-based therapies have been postulated on the basis of experimental and some early clinical data [15].

3 Cardiovascular Effects of Glucose-Lowering Medications

Cardiovascular morbidity and mortality represent the major burden in T2DM patients and the ultimate goal of T2DM treatment is to reduce the overall cardiovascular risk [16]. Studies have shown that early tight glucose control can significantly reduce cardiovascular complications in T2DM patients [3]. On the contrary, treatment intensification aiming at tight glucose control in patients with long-standing diabetes, history of poor chronic glucose control, and the presence of cardiovascular complications did not reduce cardiovascular complications and increased the risk of hypoglycemia and weight gain [17, 18]. Cardiovascular side effects have also been a major concern of several antidiabetic and anti-obesity medications eventually leading to withdrawal of some of them from the market [19, 20]. Numerous studies have shown that both hypoglycemia and weight gain commonly seen with various glucose-lowering medications such as sulfonylureas, glinides, and insulin are associated with increased risk of cardiovascular complications [18, 21]. On the contrary, incretin-based therapies carry very low risk of hypoglycemia and do not increase body weight [22, 23].

4 Cardiovascular Effects of Incretin-Based Therapies

Preclinical and small clinical studies have shown that GLP-1 has numerous beneficial effects on the cardiovascular system including the reduction of blood pressure, the improvement of lipid profile, the amelioration of endothelial dysfunction, and the postulated direct cardioprotection in experimental models of ischemia/reperfusion [24, 25]. The first clinical study suggesting the positive effects of the GLP-1 receptor agonist exenatide on reperfusion injury in patients with ST-segment elevation myocardial infarction has been published [26]. Therefore it has been generally predicted that incretin-based therapies will have either neutral cardiovascular effects or will confer cardioprotective effects in larger prospective cardiovascular trials. These optimistic expectations were mechanistically based on the experimental reports describing the widespread presence of GLP-1 receptor in the heart and the vasculature [27, 28]. Therefore the postulated cardioprotective effects could arise from the combination of indirect actions (e.g., improvement glucose control, circulating lipids, low risk of hypoglycemia) and direct effects of GLP-1 through GLP-1 receptors in the heart and vasculature. Nevertheless, the recent paper by Pyke et al. [29] revealed that with the use of specific antibody, GLP-1 receptor could only be detected in the sinoatrial node but not in the rest of the myocardium with very little presence of GLP-1 receptor in the vasculature. This sinoatrial node localization of GLP-1 receptor appears to be in agreement with the slight increase in heart rate generally seen with the use of GLP-1 receptor agonists [30]. Alternatively, heart rate increase could be partially explained as a compensatory response to decreased blood pressure by the effects of GLP-1 receptor agonists on peripheral vascular resistance, renal sodium excretion, or other yet unknown mechanisms. In contrast, no changes in heart rate have been noted in most of the studies with DPP-4 inhibitors [31, 32]. Taken

together, from the preclinical and the small clinical studies both GLP-1 receptor agonists and DPP-4 inhibitors were regarded as safe from a cardiovascular point of view. Preliminary analyses of cardiovascular endpoints within phase III trials also suggested either neutral or positive effects on cardiovascular outcomes for both DPP-4 inhibitors and GLP-1 RA [33].

As a result of modified US Food and Drug Administration (FDA) criteria for cardiovascular safety of novel glucose-lowering therapies [34], most of the incretin-based drugs are also being studied within prospective trials in patients with high cardiovascular risk or already present cardiovascular complications to corroborate their safety in this high-risk population. Two of the studies with DPP-4 inhibitors alogliptin (the EXAMINE trial) and saxagliptin (the SAVOR TIMI trial) have been concluded and the results were published in 2013 [35, 36]. In both studies, the composite cardiovascular endpoint (composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal ischemic stroke) in patients treated with alogliptin or saxagliptin did not significantly differ from the comparator (standard non-incretin-based treatment) group suggesting cardiovascular neutrality. In the SAVOR TIMI trial, slight increases in hypoglycemia rate (predominantly in patients having saxagliptin in combination with sulfonylureas) and in a number of patients hospitalized for heart failure have been noted in the saxagliptin cohort [36]. No significant increase in these parameters has been seen in the EXAMINE trial with alogliptin. A recently published meta-analysis of 84 trials concluded that the use of DPP-4 inhibitors could be associated with a slightly increased risk of heart failure [OR 1.19 (1.03; 1.37); $p = 0.015$] [37]. Another recent meta-analysis of pooled data from 20 clinical trials that included 9,156 patients on saxagliptin monotherapy or in combination with metformin did not find any increase in cardiovascular endpoint including heart failure [38]. The incidence rate ratio for heart failure in this meta-analysis was 0.55. Taken together, it is currently unclear whether there is a causal relationship between saxagliptin and/or other DPP-4 inhibitors treatment and heart failure. Other large trials with DPP-4 inhibitors (sitagliptin and linagliptin) that are currently ongoing and long-term observational studies including the program of observational safety studies planned for saxagliptin [39] will shed more light onto this question. Several potential mechanisms for worsening of heart failure by DPP-4 inhibitor treatment have been suggested including the changes of concentrations of other factors than GLP-1 by DPP-4 inhibition (e.g., B-type natriuretic peptide) and the interaction between ACE inhibitors and DPP-4 inhibitors [40]. On the contrary, experimental and small clinical trials have described an improvement in heart failure symptoms and left ventricular ejection fraction after acute or chronic treatment with intravenous or subcutaneous GLP-1 infusion [41, 42].

5 Incretin-Based Therapies and Surrogate Markers of Cardiovascular Risk

Numerous trials and meta-analyses explored the changes of surrogate cardiovascular risk factors in patients treated with incretin-based therapies. It has been found that GLP-1 receptor agonists consistently decrease blood pressure, fasting and postprandial lipid levels, and body weight [30, 43]. The only cardiovascular side effect that has been noted with GLP-1 receptor agonists is a slight increase in heart rate [30]. This increase was about 1–1.5 beats/min with shorter half-life GLP-1 RA such as exenatide BID and 2–3 beats/min with longer half-life GLP-1 RA such as liraglutide or exenatide once weekly [30]. Whether this small increase in heart rate may have any negative cardiovascular consequences in the long term when combined with positive effects of these drugs on the surrogate cardiovascular risk markers needs to be further determined. There are several ongoing long-term cardiovascular trials with different GLP-1 RA that shall be concluded within the next couple of years that should directly answer the question of cardiovascular safety/potential cardioprotective effects of GLP-1 RA.

In contrast to GLP-1 RA, DPP-4 inhibitors generally do not affect blood pressure, heart rate, or body weight [31]. In most of the studies they have either slight positive or neutral effects on fasting lipid levels and positive effects on postprandial hyperlipidemia [44, 45].

6 Pancreatic Effects of Incretin-Based Therapies

The progressive decline of β-cell number throughout the course of T2DM represents the major reason for long-term worsening of its control and the need for treatment intensification [46]. It is estimated that over 50 % of T2DM patients will require insulin therapy within 5 years of diagnosis [47]. The β-cell protection or optimally β-cell regeneration may thus markedly alter the progressive course of type 2 diabetes and improve its long-term outcomes.

Preclinical studies in rodent models have suggested that GLP-1 treatment stimulates insulin secretion, replenishes β-cell insulin stores, and prevents exhaustion of β-cell reserves via increased insulin mRNA stability [48]. Studies have also documented that GLP-1 stimulates β-cell proliferation and neogenesis and inhibits β-cell apoptosis in both normal and diabetic rodents of younger age [49, 50],

while most of the studies did not support such stimulatory effects in older rodents [51]. According to earlier studies, GLP-1 receptor is also present in rodent pancreatic ductal and acinar cells and its stimulation resulted in their differentiation towards islet-like phenotypes [52, 53]. Further experimental studies with both DPP-4 inhibitors and GLP-1 RA have documented their protective effect on β-cells against apoptosis and even increase in β-cell mass [54, 55]. While these potential benefits of incretin-based therapies were intensively studied [56], the putative proliferative effects of DPP-4 inhibitors and GLP-1 RA have also raised concerns with respect to the potential of incretin-based therapies to increase the risk of pancreatic cancer [57]. Another potential side effect that has emerged from some experimental studies and case reports was an increased risk of pancreatitis [58].

7 Incretin-Based Therapies, Pancreatitis, and Pancreatic Cancer

Studies have shown that patients with T2DM generally have an increased risk of both pancreatitis [59] and pancreatic cancer [60] compared to the non-diabetic population owing to more frequently present risk factors such as obesity, dyslipidemia, and also other underlying mechanisms that are not well understood. Most of the preclinical studies in rodents reported no evidence of either pancreatitis [61–63] or cancer lesions [64] with GLP-1 agonist or DPP-4 inhibitor treatment. In contrast, in human islet amyloid polypeptide transgenic rats, a model of type 2 diabetes, sitagliptin plus metformin had synergistic effects on β-cell mass preservation, but sitagliptin treatment was associated with increased pancreatic ductal turnover, ductal metaplasia, and, in one rat, pancreatitis [65]. The authors concluded that adverse actions of sitagliptin treatment on exocrine pancreas raise concerns that require further evaluation.

In another recent paper, high fat diet-fed mice treated with exenatide or sitagliptin had more pronounced acinar cell injury (hypertrophy, autophagy, apoptosis, necrosis, and atrophy), vascular injury, interstitial edema and inflammation, fat necrosis, and duct changes compared to the control group [66]. Taken together, experimental data are inconsistent although the majority of the studies did not report either induction of pancreatitis or pro-proliferative effects in the direction of pancreatic cancer. Nevertheless, it is important to note that significant differences in GLP-1 receptor localization in the pancreas may exist between rodents and primates or humans, respectively. Furthermore, widespread GLP-1 receptor expression described in previous reports in rodent pancreas could have been due to use of non-specific GLP-1 receptor antibodies. Indeed, Pyke et al. [29] have shown using a new specific monoclonal anti-GLP-1 receptor antibody that in pancreata of primates and humans the GLP-1 receptor was only present in insulin-producing cells but not in duct epithelial cells. Waser et al. [67] recently showed high GLP-1 receptor expression in insulin- and somastostatin-producing cells of normal human pancreas, little GLP-1 receptor expression in acinar cells, and no expression in ductal epithelial cells. Increased duct epithelial cell proliferation is one of the initial events involved in early stages of pancreatic cancer development [60].

Pancreatitis as a potential side effect of GLP-1 RA exenatide has been reported as case reports in the literature [58] and the FDA has also reported documented cases of pancreatitis in patients taking the DPP-4 inhibitor sitagliptin [68]. Elevations of lipase and amylase levels after treatment with incretin-based therapies have been described [69]. Nevertheless, it is also important to note that significant number of patients with type 2 diabetes without incretin-based therapies have higher lipase and/or amylase levels than the upper normal limit with no signs of acute pancreatitis [70]. Elashoff et al. [71] used the FDA adverse event reporting system (AERS) database to explore the rates of reported pancreatitis, pancreatic and thyroid cancer, and all cancers associated with sitagliptin or exenatide, compared with other glucose-lowering therapies. In their analysis, the use of sitagliptin or exenatide increased the odds ratio for reported pancreatitis sixfold as compared with other therapies and pancreatic cancer was more commonly reported among patients who took sitagliptin or exenatide as compared with other therapies. Elashoff's study has been widely criticized because of the significant limitations or even complete impropriety of the AERS database for this type of analysis, a clear influence of publicity linking specific drugs to reports of adverse events and numerous other reasons [72]. Other studies using other sources and databases such as the Aperio Administrative Health Claim Database and Normative Health Information Database did not see increased rates of pancreatitis with exenatide or sitagliptin, respectively [73, 74]. Two recently published meta-analyses also did not suggest an increased risk of pancreatitis with incretin-based therapies [75, 76]. Furthermore, in the two prospective cardiovascular randomized trials with DPP-4 inhibitors no differences in the rate of pancreatitis and pancreatic cancer were found between saxagliptin and alogliptin and control groups, respectively [35, 36, 77]. Recent pooled analysis of pancreatitis in phase III trials with incretin-based therapies that have used the data provided by pharmaceutical companies or obtained by literature search have found an OR of 1.39 (95 % CI 0.67, 2.88) for GLP-1 receptor agonists and OR of 1.07 (95 % CI 0.72, 1.58) for DPP-4 inhibitors suggesting a slight trend towards increased risk with GLP-1

receptor agonists [78]. In a recently presented safety analysis of patients treated with liraglutide 3.0 mg/day within the SCALE Obesity and Prediabetes randomized trial, gallbladder-related adverse events and frequency of pancreatitis were higher with liraglutide vs. placebo (2.5 vs. 1.0 % and 0.3 vs. 0.1 %, of patients, respectively) [79]. Taken together, a slightly increased risk of pancreatitis could be seen in some of the studies with GLP-1 receptor agonists, while no such trend is apparent with DPP-4 inhibitors.

The lack of morphological data from human pancreatic tissue and the need for long-term observational studies do not enable one to make final conclusions regarding incretin-based therapies and pancreatic cancer. Butler et al. [80] have shown that the presence of obesity and type 2 diabetes increases the turnover of ductal pancreatic cells which is a known risk factor for pancreatic cancer. They have also proposed that incretin-based therapies may induce a low grade chronic pancreatitis and that the combination of these risk factors may eventually in the long-term run increase the risk of pancreatic cancer [81]. To support their hypothesis based on the experimental rodent findings, they examined the pancreata from organ donors with type 2 diabetes mellitus treated by incretin-based therapy or other therapy and non-diabetic control subjects using samples obtained from the Network for Pancreatic Organ Donation [82]. Their study has shown an approximately 40 % increased pancreatic mass in patients treated with incretin-based drugs owing to both increased exocrine cell proliferation and dysplasia. They also describe an α-cell hyperplasia and glucagon-expressing microadenomas in three of eight patients treated with incretin-based therapy. The study has sparked a lively discussion in the scientific and medical community with some expressing concerns with respect to the safety of patients treated with incretin-based therapies [83]. Bonner-Weir et al. [84] have reexamined Butler's data in detail and concluded that "the original data presented in Butler's paper had serious methodological deficiencies that preclude any meaningful conclusions". The major concerns were mismatched age distribution between the groups, questionable diagnosis of type 2 diabetes in some of the patients, extreme outlier cases responsible for pancreatic weight differences, methodological problems with quantification of both α- and β-cells and microscopic noninvasive epithelial neoplasm within the pancreatic ducts (PanINs) [84]. In February 2014, the FDA and European Medicines Agency (EMA) published a common statement on pancreatic safety of incretin-based drugs [85]. The statement was based on a complex reevaluation of multiple streams of data starting from toxicological findings in healthy and diabetic animals and human data from both observational and outcome trials and multiple clinical safety databases. In this statement, the two agencies concluded that "assertions concerning a causal association between incretin-based drugs and pancreatitis or pancreatic cancer, as expressed recently in the scientific literature and in the media, are inconsistent with the current data". Nevertheless, according to both agencies the final conclusion regarding a causal relationship could not be reached and pancreatitis will continue to be considered a risk associated with these drugs until more data are available.

8 Conclusions and Practical Considerations

At the moment, cardiovascular safety of incretin-based therapies still needs to be definitely confirmed by prospective cardiovascular trials, most of which are still ongoing. Overall, it can be concluded that the majority of the current data suggest good a cardiovascular safety with some open questions awaiting final answers. The two concerns that have been raised in the cardiovascular side effects area are a slight increase in heart rate with GLP-1 RA treatment and a potentially increased risk of heart failure with saxagliptin and possibly other DPP-4 inhibitors. Both of these issues certainly need further studies and explorations, and the ongoing prospective cardiovascular trials and long-term observational studies should provide more definite answers. Nevertheless, at the moment no specific limitations with regards to these potential side effects appear to be justified by the available data and no limitations in this regard are included in the treatment guidelines.

The pancreatic safety of incretin-based therapies has been extensively evaluated by both the FDA and EMA regulatory agencies and their view was clearly described in their statement published in the *New England Journal of Medicine* in 2014. The causal interrelationship between pancreatic cancer and DPP-4 inhibitors or GLP-1 receptor agonists does not appear to be supported by the current clinical data. A recent pooled analysis of phase III studies including both published data and unpublished results provided by pharmaceutical companies suggested a possibility of a slight increase of pancreatitis risk with GLP-1 receptor agonists but not DPP-4 inhibitors treatment. At the same time, it is necessary to bear in mind that the risk of acute pancreatitis and pancreatic cancer is significantly higher in patients with T2DM relative to non-diabetic subjects regardless of the mode of treatment. Potential pancreatic side effects still remain under the close surveillance and scrutiny of both clinicians and regulatory agencies. At the moment, neither DPP-4 inhibitors nor GLP-1 receptor agonists are recommended for use in patients with a history of acute pancreatitis or pancreatic cancer. Also, the treatment with GLP-1 RA or DPP-4

inhibitors should be withdrawn in patients with clinical or laboratory symptoms of acute pancreatitis.

In summary, the discovery of incretin-based therapies has undoubtedly opened new avenues in the treatment of type 2 diabetes owing to their good efficacy and complex positive effects beyond glucose control. Although some safety issues with respect to both pancreatic and cardiovascular side effects still need further exploration, current clinical data do not raise major concerns that would justify further prescription limitations or other measures.

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