Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Articles from the Incretin Hormones and Incretin-based Glucose-lowering Medications Special Issue, Edited by Michael Nauck, Manfredi Rizzo and Christos Mantzoros

Incretin-based therapies in 2021 – Current status and perspectives for the future

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It has generally been accepted that diabetes increases significantly morbidity and mortality but during the current pandemic diabetes has attracted particular attention since its presence has been associated with the most severe forms of COVID-19 and related mortality [1,2]. It's therefore of crucial importance to keep diabetic patients under proper management not only to control short term complications and to prevent liver and cardio-renal-metabolic complications, but also to reduce the risk of a potentially severe course and limit adverse outcomes due to COVID-19 [3–7]. Several authors have emphasized the importance of novel anti-diabetic agents during this pandemic, such as incretin-based therapies, for patients with type-2 diabetes (T2DM) [8–10]. Dipeptidyl peptidase-4 (DPP4)-inhibitors and glucagon-like peptide 1 receptor agonists (GLP1-RAs) have the ability to support near-normoglycemic glucose control without increasing the risk for hypoglycemic episodes and most of GLP1-RAs have demonstrated significant cardio-renal benefits that help the prevention of such complications and prolonging patients' healthy lives [11,12].

This editorial is part of the special issue entitled "The role of incretin hormones and incretin-based glucose-lowering medications", containing ten publications from distinguished international experts in the field, and edited by the authors of the present article. Firstly, JJ Holst reviewed available evidence on the role of GIP and GLP-1 in the incretin system in healthy humans, concluding that both hormones act to improve glucose tolerance and that their effects are additive: GIP seems to be quantitatively the most important, particularly regarding insulin secretion, while GLP-1 action seems to be mainly displayed via inhibition of glucagon secretion [13]. Farr et al. then prepared a comprehensive and critical review of pre-clinical and clinical studies on GIP, GLP-1 and DPP4-inhibition, describing the role of the central nervous system in energy homeostasis and then the current state of knowledge on incretin physiology, pathophysiology and efficacy in such studies [14].

MA Nauck introduced the subsequent clinical articles dealing with the ups and downs during the development incretin physiology and incretin-based therapeutics like GLP1-RAs and DPP4-inhibitors for patients with T2DM, viewing it as a rollercoaster history about the use of physiological and pharmacological properties of incretin hormones to develop diabetes medications with a convincing benefit-risk relationship [15]. Alexopoulos and Buse provided a framework to guide decision-making in a real-world setting about initiating injectable therapy with GLP1-RAs vs. insulins [16], and Farngren and Ahrén summarized how incretin therapies may be one good answer related to the challenges of hypoglycaemia [17]. They suggested that such therapies should represent the treatment of choice when the therapeutic targets include avoidance of hypoglycaemia [17].

Other authors made some interesting comparisons between the different classes of novel anti-diabetic agents. Giorgino et al. reviewed and critically discussed available evidence on the efficacy and safety of GLP1-RAs vs. sodium-glucose cotransporter 2 (SGLT2)-inhibitors [18], while Stoian et al. made a similar comparison on DPP4-inhibitors vs. other oral glucose-lowering medications [19]. Sachinidis et al. critically discussed available data from cardiovascular outcome trials (CVOT) studying GLP1-RAs and DPP4-inhibitors [20], while Kokkinos et al. focused on the weight loss effects, discussing how medications that mimic gut hormones or target their receptors may eventually replace bariatric surgery [21]. Finally, Davies et al. made an excellent update on what current international recommendations suggest with respect to GLP-1 receptor agonists and DPP-4 inhibitors [22].

Recently, an international observational study involving about 10,000 T2DM patients has shown that 1/3 of them have established CVD, due to atherosclerotic CVD, consistent with earlier findings; yet, only a small proportion of these subjects were receiving glucose-lowering therapies with proven cardiovascular benefit [23]. Indeed, there is still large discrepancy between scientific evidence and clinical practice worldwide, although CVOT with the use of GLP1-RAs have shown their benefit on major adverse cardiovascular events, on their individual components (non-fatal myocardial infarction, non-fatal stroke and cardiovascular mortality), as well as on all-cause mortality, hospitalization for heart failure and kidney-related outcome (Fig. 1). On this basis, GLP1-RAs are now clearly identified by scientific guidelines as a treatment of choice for T2DM; yet, the adoption of such international recommendations is still suboptimal, and this contributes negatively to what we perceive as clinical inertia [24,25]. Since atherosclerotic CVD is predominant in T2DM patients, it should be also considered that some GLP1-RAs, such as liraglutide and semaglutide, have shown direct anti-atherosclerotic effects that help explaining the beneficial cardiovascular outcomes [26–28].

Some interesting novel findings have been discussed during the recent 81st Annual Scientific Sessions of the American Diabetes Association where, for instance, the data on efficacy, safety, and tolerability of the dual GIP and GLP-1 receptor agonist tirzepatide were presented. Tirzepatide has shown robust improvements in glycaemic control and body weight in T2DM patients, apparently with a safety/tolerability

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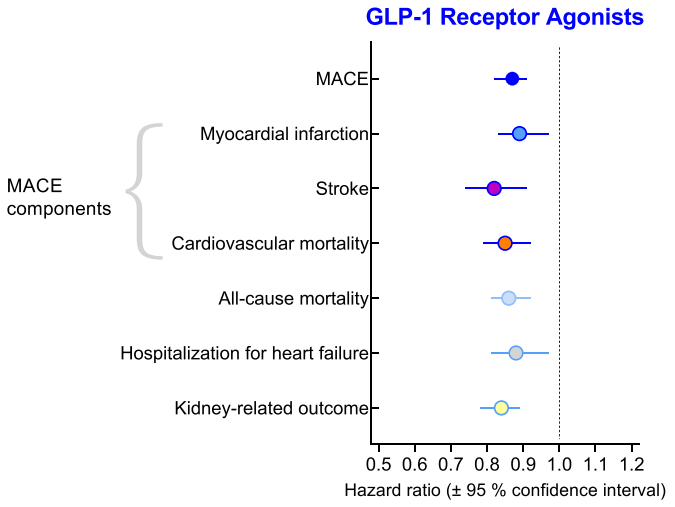

Fig. 1. Reductions in the risk for cardio-renal endpoints from cardiovascular outcome trials testing clinical effects of GLP1-RAs. The analysis is based on the respective numbers of patients reporting or not reporting an event (Fisher's exact test). The analysis published by Kristensen et al. [31] has been amended and extended: ELIXA (lixisenatide) results were not included because lack of any cardio-renal effectiveness [32]. AMPLITUDE-O results (regarding efpeglenatide) have been included [33].

profile similar to less effective GLP-1 RAs [29]. This will potentially increase the number and properties of therapeutic options we have for our patients, giving more opportunities for an individually tailored treatment. Filling the gap between guidelines and real world in the cardiometabolic approach to diabetic patients is now an urgent need, even more during current pandemic [30]. Patients with chronic diseases, such as those with diabetes and obesity, need a better management in order to prevent potential complications, especially given an overall reduced access to the usual health care facilities and specialty clinics. It is imperative to aim at preserving their liver and cardio-renal function beyond aiming for a mere gluco-metabolic control and, therefore, a more appropriate use of drugs with proven benefit, such as incretin-based therapies, has to be advocated for those who would benefit from such treatment.

Declaration of competing interest

The authors declare that the present article was written independently. MR has given lectures, received honoraria and research support, and participated in conferences, advisory boards and clinical trials sponsored by many pharmaceutical companies including Amgen, AstraZeneca, Boehringer Ingelheim, Kowa, Eli Lilly, Meda, Mylan, Merck Sharp & Dohme, Novo Nordisk, Novartis, Roche Diagnostics, Sanofi and Servier; he is full-time Professor of Internal Medicine at University of Palermo, Italy and currently Medical Director, Novo Nordisk Eastern Europe. MAN has been member on advisory boards or has consulted with AstraZeneca, Boehringer Ingelheim, Eli Lilly & Co., GlaxoSmithKline, Menarini/Berlin Chemie, Merck, Sharp & Dohme, and NovoNordisk. He has received grant support from AstraZeneca, Eli Lilly & Co., Menarini/Berlin-Chemie, Merck, Sharp & Dohme, and NovoNordisk. He has also served on the speakers' bureau of AstraZeneca, Boehringer Ingelheim, Eli Lilly & Co., Menarini/Berlin Chemie, Merck, Sharp & Dohme, and NovoNordisk. C.S.M. reports grants, personal fees, and other from AltrixBio, Coherus Biosciences, and Novo Nordisk, personal fees and non-financial support from Ansh, Aegerion, California Walnut Commission, and personal fees from Lumos, GENFIT, Intercept, Regeneron, CardioMetabolic Health Conference, The Metabolic Institute of America and Amgen. None of the above mentioned companies had any role in this article, which has been written independently, without any financial or professional help, and reflects only the opinion of the authors, without any role of the industry.

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Manfredi Rizzo
Department of Health Promotion Sciences Maternal and Infantile Care, Internal Medicine and Medical Specialties (PROMISE), University of Palermo, Italy
Division of Endocrinology, Diabetes and Metabolism, University of South Carolina School of Medicine, Columbia, SC, USA

Michael A. Nauck
Diabetes Division, Katholisches Klinikum Bochum, St. Josef Hospital, Ruhr-University Bochum, Bochum, Germany
Corresponding author at: Diabetes Division, Katholisches Klinikum Bochum, St. Josef Hospital, Ruhr-University Bochum, Gudrunstr, 56, 44791 Bochum, Germany.
E-mail address: michael.nauck@rub.de.

Christos S. Mantzoros
Department of Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA
Section of Endocrinology, VA Boston Healthcare System, Harvard Medical School, Boston, MA, USA

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