Dipeptidyl Peptidase-4 Inhibitor Development and Post-authorisation Programme for Vildagliptin –

Clinical Evidence for Optimised Management of Chronic Diseases Beyond Type 2 Diabetes

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T he last decade has witnessed the role of dipeptidyl peptidase-4 (DPP-4) inhibitors in producing a conceptual change in early management of type 2 diabetes (T2DM) by shifting emphasis from a gluco-centric approach to holistically treating underlying pathophysiological processes. DPP-4 inhibitors highlighted the importance of acknowledging hypoglycaemia and weight gain as barriers to optimised care in T2DM. These complications were an integral part of diabetes management before the introduction of DPP-4 inhibitors. During the development of DPP-4 inhibitors, regulatory requirements for introducing new agents underwent substantial changes, with increased emphasis on safety. This led to the systematic collection of adjudicated cardiovascular (CV) safety data, and, where 95% confidence of a lack of harm could not be demonstrated, the standardised CV safety studies. Furthermore, the growing awareness of the worldwide extent of T2DM demanded a more diverse approach to recruitment and participation in clinical trials. Finally, the global financial crisis placed a new awareness on the health economics of diabetes, which rapidly became the most expensive disease in the world. This review encompasses unique developments in the global landscape, and the role DPP-4 inhibitors, specifically vildagliptin, have played in research advancement and optimisation of diabetes care in a diverse population with T2DM worldwide.

Today, almost 90 years after La Barre and Still first described the physiological effects of a substance they later named 'incretin',[1] therapies based on such gastrointestinal peptides have become an integral part of type 2 diabetes (T2DM) management. The discovery of the insulinotropic role of incretins and their impact on the entero-insular axis,[2,3] were soon followed by a conclusion that glucagon-like peptide-1 (GLP-1) was the most potent incretin in humans.[4] Its ability to normalise glucose levels in people with T2DM without risk of hypoglycaemia, was subsequently established, highlighting its clinical potential.[5] The discovery of dipeptidyl peptidase-4 (DPP-4)[6] and its role in the degradation of GLP-1[7] provided the foundation to augment treatment of diabetes.[8] In 1998 a compound now known as vildagliptin was synthesised and its entry into early clinical trials in human subjects marked a point when its unique journey from a conceptual discovery to causing a revolutionary change in management of T2DM commenced.[9–11]

Management of type 2 diabetes at the turn of the twentieth century

Before discussing the development of DPP-4 inhibitors further, however, the contemporaneous setting of treatment for diabetes must be considered. The UK Prospective Diabetes Study (UKPDS)[12] had reported an unexpectedly dramatic effect of hypertension management, whilst conventional glycaemic control had failed to reduce mortality due to major cardiovascular (CV) events, whereas metformin, only recently licensed in the US, had reduced mortality and T2DM-related outcomes.[13] The first thiazolidinedione —troglitazone —had been licensed, launched and withdrawn.[14,15] Despite its short time on the shelves, it had contributed substantially to understanding the aetiopathogenic 'triumvirate' of impaired pancreatic insulin secretion and insulin resistance in the muscle and liver.[16,17] The subsequent 10 years witnessed the introduction of rosiglitazone and pioglitazone, followed by the

temporary suspension of rosiglitazone due to a perceived increase in CV risk.[18] Subsequently, the US Food and Drug Administration (FDA) mandated companies to empirically demonstrate CV safety for all new anti-hyperglycaemic agents. This came juxtaposed with the ACCORD (NCT00000620) study demonstrating a lack of benefit and possible increase in CV risk from intensive glycaemic control in patients with long-term sustained hyperglycaemia.[19] ADVANCE (NCT00949286)[20] and VADT (NCT00032487)[21] did not show a corresponding increase in cardiac death, nor did they demonstrate any substantial reductions in diabetes-related events.[20] Nevertheless, a paradigm shift had arrived; from targeting aggressive glucose lowering to avoiding adverse events, such as hypoglycaemia and weight gain with a significant adverse metabolic impact. This was only possible due to the introduction of pharmacological interventions, restoring the natural physiology of glucose regulation. Indeed, it was only through the longer-term studies that these events were determined to be adverse drug reactions rather than inevitable complications of progressive T2DM. Introducing the new composite outcome, percentage of patients achieving glycaemic target without weight gain and hypoglycaemia soon became the standard in studies of DPP-4 inhibitors and subsequent new classes.[22–25]
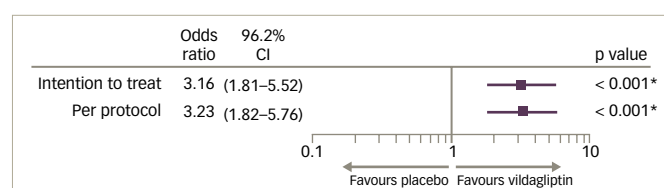
As a class, the DPP-4 inhibitors were the first agents required to abide by the new FDA and European Medicines Agency (EMA) regulatory requirements to demonstrate CV safety. A unique feature of the vildagliptin development programme had been the independent adjudication of all CV events, enabling a systematic meta-analysis even prior to the mandate reflecting the same requirements. The remaining DPP-4 inhibitors were requested to demonstrate CV safety after receiving regulatory (provisional) approval. Interestingly, demonstrating CV safety in high-risk individuals, with dedicated CV outcomes trials (CVOT), proved more formidable than the previous studies targeting a benefit. The DPP-4 inhibitors established new standards for the design and endpoints of CVOT safety studies and demonstrated the strain in meeting the criteria for a systematic meta-analysis. The standardisation of major adverse CV events (MACE) resulted in the three-factor composite outcome of cardiac death, non-fatal myocardial infarction and non-fatal stroke. This '3-point MACE' excluded a fourth potential event, hospitalisation for acute coronary syndrome, due to its subjective nature. In order to achieve the stipulated tight confidence intervals (CI) required to demonstrate CV safety,[26] these studies became a massive undertaking in terms of resources. Many questioned the relevance of such investment, which was inevitably reflected in the cost of the agents, merely to demonstrate non-inferiority compared with placebo, rather than more clinically relevant explorations of methods to improve the care of people with diabetes.[27] For example, the trial evaluating CV outcomes with sitagliptin (TECOS; NCT00790205) study enrolled 14,671 patients over several years to demonstrate sitagliptin usage had exactly the same CV event rates as placebo in addition to conventional care, with a hazard ratio of 1.0 and 95% CI of 0.83–1.20.[28]

New standards, new populations

In addition to the CV safety requirements, the growing worldwide burden of T2DM presented new socio-economical, psychological and cultural challenges for the development of drugs. It was no longer sufficient simply to demonstrate a favourable benefit–risk ratio for DPP-4 inhibitors within the typical Western European or American populations of the ACCORD,[19] ADVANCE,[20] and VADT[21] trials, or even different ethnicities[29] but the clinical utility of the class was to be established in populations united by characteristics beyond pathophysiology, namely cultural and religious habits.

Globally, there are 148 million people with diabetes who follow Islam and up to 80% of them fast during the Holy month of Ramadan every

Figure 1: Odds ratio for proportion of elderly patients achieving individualised HbA1c targets after 24 weeks

*The odds ratios, p values, and associated CI were calculated from a logistic regression model. *Indicates statistical significance at two-sided 3.8% level. CI = confidence interval.*

year.[30] Long periods of fasting and extreme changes in nutrition and fluid intake, during fasting and feasting, leads to a 7.5-fold increased risk of severe hypoglycaemia during the Holy month compared with non-fasting months.[31] The advent of agents' physiologically controlling hyperglycaemia with a low risk of hypoglycaemia enabled, for the first time, fasting Muslims to have symptomatic benefit of better glucose control without the devastating consequences of hypoglycaemia. An audit the year after the launch of vildagliptin demonstrated an 87% reduction in hypoglycaemic episodes compared with the standard care at the time, gliclazide,[32] triggering a series of observational studies[33,34] and a subsequent interventional study.[35] Studies demonstrated a distinct reduction in hypoglycaemia compared with gliclazide or all sulphonylureas (SUs), for vildagliptin and sitagliptin,[36] respectively; although in an *a priori* analysis of sitagliptin compared to gliclazide, there was no difference in hypoglycaemia.[36] As a result, DPP-4 inhibitors became the recommended treatment of choice for people preparing for Ramadan.[37]

Managing diabetes in older adults

Older adults are fundamentally different in terms of their responses to stimuli, whether external, endocrine or paracrine, from younger adults. Despite an acceptance of these variances, older adults were routinely excluded from earlier interventional studies. Worldwide, almost a third of the population with diabetes are over the age of 65,[38–40] many of whom are undiagnosed.[41] In institutional care, this undiagnosed population rises to approximately one in four.[41] The high prevalence of T2DM in the very elderly is excluded from the worldwide estimates,[42] likewise, these patients are mostly excluded from clinical trials.[43,44]

The INdividualising Targets for EldeRly patient using Vildagliptin as Add-on or Lone therapy (INTERVAL) study was the first to not only demonstrate safety and efficacy of DPP-4 inhibitors exclusively in older adults beyond the age of 70 (with no upper limit), but also to explore the processes and the success of personalised target setting.[45] In this elderly cohort, in which the oldest patient was 97 years old, the adjusted odds ratio of achieving the individualised targets was 3.16 (96.2% CI 1.81–5.52; p<0.0001) (see *Figure 1*) in favour of vildagliptin. Surprisingly, men were set more aggressive targets than women (p=0.026; *Figure 2*), whereas setting targets according to the frailty status demonstrated only a trend towards significance (p=0.068). In non-frail patients, the baseline weight predicted a less aggressive glycemic target setting (p=0.012), while astonishingly, glycaemic targets were not adjusted according to the body weight in frail patients (p=0.725; *Figure 3*).

The INTERVAL study was conducted before any national guidelines advocated individualising therapeutic goals. While demonstrating a similar tolerability and glycaemic efficacy in older adults, as had previously been demonstrated for younger adults, it paradoxically reported that physicians' target setting was predominantly driven by local guidance and baseline glycated haemoglobin (HbA1c), rather than
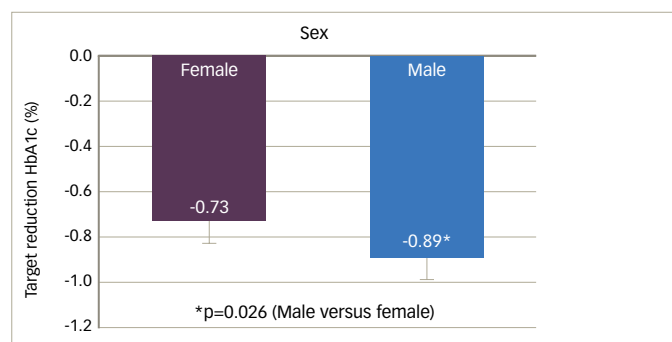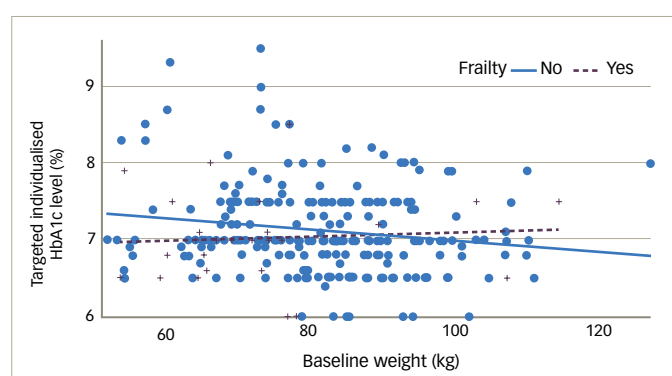
Figure 2: Sex status versus target reduction HbA1c

Figure 3: Baseline weight versus targeted individualised HbA1c by frailty status

Figure 3: Baseline weight versus targeted individualised HbA1c by frailty status

demonstrated lack of progressive loss of eGFR over time versus placebo: annual eGFR change following vildagliptin and placebo treatment was -1.62 and -1.80 ml/min/1.73 m^2, -1.98 and -2.44 mL/min/1.73 m^2 in patients with moderate and severe renal impairment, respectively.[53]

The clinical utility and safety of other DPP-4 inhibitors was similarly demonstrated with appropriate dose reductions (with the exception of linagliptin which requires no dose adjustment due to its hepatic excretion) due to tendency towards an increased C_{max}.[22–25,54–56] It is, however, important to recognise that the non-renal excretion did not make linagliptin any more safe than other DPP-4 inhibitors as its fundamental mechanism of action is similar.[57] However, a *post hoc* meta-analysis with linagliptin initially suggested a glucose-independent reduction in albumin excretion rate (AER) of 32%,[58] originally hypothesised due to a direct anti-inflammatory effect of the molecule's xanthine ring. Nevertheless, a mechanistic study with vildagliptin demonstrated a similar 44% reduction in AER over an 8-week period.[59] Similarly, the CVOTs of other DPP-4 inhibitors demonstrated a greater AER reduction than placebo, despite glycaemic equipoise.[60,61] The reduction in AER is presumably a direct effect of active GLP-1 on the renal receptors, supported by the reduction in micro- and macroalbuminuria in the LEADER (NCT01179048) study.[62] The MARLINA (NCT01792518) study, however, comparing linagliptin to placebo in those with pre-existing renal impairment, failed to confirm a glucose-independent benefit.[63]

Clinical experience with dipeptidyl peptidase-4 inhibitors in the real-world

Randomised controlled trials (RCTs) have high internal validity, enrol selected, highly motivated subjects with few, but optimally managed co-morbidities, and tend to run over a short time frame in developed countries with frequent and prolonged follow-up visits. The launch of DPP-4 inhibitors coincided with increasing awareness of the disparity between the results from RCTs and the efficacy observed in the general clinical practice; highlighting an unmet need to explore the use of the newer agents in more diverse populations worldwide, in presence of co-morbidities, over a longer period in 'real-world' and variable resource settings.

The first, and most comprehensive real-world study with a DPP-4 inhibitors was the Effectiveness of Diabetes control with vildaGliptin and vildagliptin/mEtformin (EDGE) study, enrolling over 45,000 patients in 27 countries and 5 regions.[64] This study uniquely represented the worldwide, everyday challenges of managing diabetes. Investigators chose to intensify the failing monotherapy, at their discretion, based on parameters they considered relevant, introducing comparators to dual therapy with vildagliptin consisting mostly of metformin-SU or metformin-pioglitazone combinations. Rather unexpectedly, the DPP-4 inhibitor was not only providing the expected HbA1c reduction of 1.19% over 12 months but also demonstrating superiority at every time point over the year, predominantly due to 'underperformance' of the comparators, mostly SUs.[65] This divergence between the RCT data and real-world evidence was potentially induced by slow titration implemented for SUs, from initiation to optimal target dose in keeping with routine clinical practice. Further, under-diagnosed hypoglycaemia in this real-world setting contributed to under-recognised non-adherence.

The EDGE study also validated the role of real-world evidence for demonstration of regional differences,[66] lack of extensive epidemiological data around hotspots of T2DM[67] and, most of all, magnitude of clinical inertia affecting second-line therapy intensification.[67] Physician preferences,[68] gender discrimination and regional differences in

age, frailty or co-morbidities.[46] This was despite intensive training on holistic assessment and individualising care on a frail elderly population up to the age of 97.[45,46]

Managing the ultimately challenging populations with type 2 diabetes – those with renal disease

The launch of DPP-4 inhibitors coincided with the introduction of the National Kidney Foundation (NKF) Kidney Disease Outcomes Quality Initiative (NKF KDOQI) characterisation of T2DM and renal disease, which acknowledged that almost a third of people with diabetes had some degree of nephropathy characterised by proteinuria and/or a reduced estimated glomerular filtration rate (eGFR).[47] The identification of these individuals dramatically limited the potential therapeutic options, given metformin, alpha-glucosidase inhibitors, and the majority of SUs were contraindicated. The associated weight gain and fluid retention with pioglitazone, although licensed, made it a less attractive therapeutic alternative for people with renal impairment and the use of short-acting insulins and SUs in those with reduced eGFR significantly increases the risk of hypoglycaemia due to unpredictable accumulation.[48] The physiological action of DPP-4 inhibitors, however, provided a suitable alternative to be explored in renal impairment. As a result, detailed pharmacokinetic (PK) studies were performed with all agents,[49] followed by clinically meaningful studies, even in high doses, particularly in Asian patients undergoing haemodialysis.[50]

The PK profile of vildagliptin demonstrated reassuringly a very similar maximum serum insulin concentration (C_{max}) but doubling of exposure in those with moderate to severe renal impairment. This allowed a reduction in dosing frequency to once daily, while retaining equivalent glycaemic benefits, for effectively half the price.[51–53] And as predicted, similarly to the other DPP-4 inhibitors, a large, randomised, one-year trial

prescription habits for newer but also older oral anti-diabetes drugs (OADs) or worldwide resistance to insulin initiations[69] were also some of the key findings of EDGE. Simultaneously, EDGE has provided a unique foundation for cost-effectiveness analyses with patient-level data.[70] These data were instrumental in assessing the health economic (HE) value of the DPP-4 inhibitors worldwide without simulations and modelling based on RCTs.
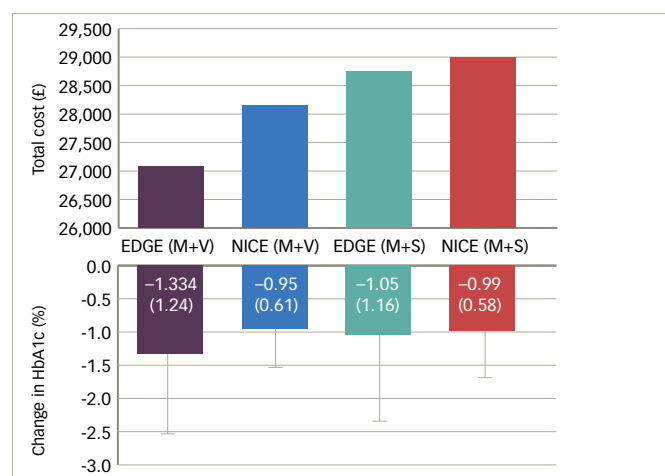
Health economics in the real-world setting

The launch of the DPP-4 inhibitors coincided with the global recession of 2007, which substantially changed the HE approach for newer drugs. Traditionally, cost-effectiveness evaluations were based on HbA1c reductions in RCTs and the relative value of such extrapolated from UKPDS data. This practice, however, often did not capture the differences in demographics, clinical profiles, motivation, socio-economic and cultural factors in the real-world.[71] Further, the RCT data were predominantly placebo-controlled, which did not allow for direct inter-agent comparisons. The availability of patient-level data from a real-world setting enabled HE models to implement improved external validity, mimicking the EDGE study, and perform inter-drug comparisons between DPP-4 inhibitor and the then standard of care, SU. The estimated total costs, and change in HbA1c between baseline and one year estimates for metformin in combination with either vildagliptin or sulphonylureas as per the EDGE and National Institute for Health and Care Excellence approaches are summarised in *Figure 4*. The results suggested that guidelines basing their estimates on data from RCTs may underestimate the health economic value of modern treatments such as DPP-4 inhibitors.[72] Furthermore, real-world data suggested vildagliptin would be associated with a reduction in the cumulative incidence of major micro- and macrovascular complications, increase in quality-adjusted life expectation and delaying the need for insulin,[73,74] all principle drivers of expenditure in diabetes.[75–77] It is important here to differentiate between the most frequent real-world use of DPP-4 inhibitor (i.e. as an early add-on mostly to metformin and in people with a relatively low CV risk) versus secondary preventative profile addressed in the CVOTs, as early treatment intensification and reduction in HbA1c without weight gain or hypoglycaemia would translate into the ultimate treatment goal: long-term prevention of complications of diabetes.

The future of diabetes, with dipeptidyl peptidase-4 inhibitors

Over the last decade, DPP-4 inhibitors have played a critical role in the innovative design of and advance in clinical trials, setting standards for both RCTs and non-interventional studies and in new, diverse populations living with T2DM.[64,78] Nevertheless, several past paradigms based on historical studies, such as the UKPDS, still define and set standards for expectations managing people with diabetes in a stepwise manner. In addition, the persistently progressive nature of the underlying disease, partially attributable to the non-modifiable risk factors, but also current diabetes treatment paradigm characterised by ineffective lifestyle interventions, followed by (often delayed) monotherapy and frequent early treatment failure with prolonged periods of sustained hyperglycaemia, become inevitable consequences of sequential clinical inertia. Thus, it is most appropriate to re-think the current treatment paradigm for T2DM in the context of a more aggressive initial therapy; specifically with early initiation of combination therapy addressing the key pathophysiological defects driving the underlying disease.

The Vildagliptin Efficacy in combination with metfoRmIn For earlY treatment of T2DM (VERIFY) study explores the clinical benefits of

Figure 4: Summary of total cost, and change in HbA1c of metformin + vildagliptin and metformin + sulphonylurea using NICE and EDGE approaches

M+S = metformin + sulphonylurea; M+V = metformin + vildagliptin; NICE = National Institute for Health and Care Excellence.

early combination in 2,000 newly diagnosed people with T2DM and mild hyperglycaemia (HbA1c between 6.5% and 7.5% at baseline) by comparing a monotherapy strategy based on metformin, established standard of care, with early combination of vildagliptin and metformin.[79] Initiating dual therapy from the outset, the results will determine whether this translates into durability and long-term benefits such as delayed time to initial treatment failure or time to insulin. For the first time, an extended follow-up of this study will explore the potential benefit of the aggressive early intervention compared to the more 'real-world' approach plagued with clinical inertia. VERIFY will, in addition, explore early changes in the vasculature of patients with T2DM, thus addressing primary clinical objective for treatment of hyperglycaemia. The results of VERIFY will be reported in 2019.[80]

Failure to escalate therapy, when appropriate, has been an unfortunate feature of diabetes management for many years.[81] Indeed, today in the UK only one in five people achieves adequate glycaemic, blood pressure and lipid control, leading to as many as 24,000 premature unnecessary deaths a year.[1,82] The advent of well-tolerated statins and modern anti-hypertensive agents have accelerated improvements in care, however, glycaemic control has remained a hurdle to optimised care. This is, in part, due to the tolerability issues, weight gain and hypoglycaemia associated with traditional treatment alternatives. These adversely affect quality of life by approximately the same degree as is gained by improving HbA1c by 1% (11 mmol/mol), and therefore affect adherence to the hypoglycaemic regimen.[83] The late introduction and escalation of agents, however, may be even more detrimental, with hyperglycaemia causing early epigenetic changes that perpetuate vascular inflammation long after glucose has been brought under control.[84] Thus, access to well-tolerated agents via sustainable access programmes,[85] not limited to DPP-4 inhibitors such as vildagliptin, may provide benefits beyond the direct impact of their anti-hyperglycaemic effect by removing one of the principle barriers to appropriate escalation of care.

Evidently, treatment optimisation is only applicable where the agents with acceptable benefit–risk ratio are affordable and accessible. The International Diabetes Federation (IDF) estimates that 86% of young adults with diabetes live in low- and middle-income countries (LMICs)

where poverty, lack of education and low health system resources co-exist.[86] Nearly 75% of global premature deaths due to non-communicable diseases (NCDs) occur in these LMICs.[86]

Conclusions

The last decade has witnessed the DPP-4 inhibitors take centre stage, especially in the early management of T2DM. They produced a conceptual change in disease management, with the emphasis moving from a gluco-centric approach to treating the underlying pathophysiological processes. During their development, DPP-4 inhibitors pioneered the mechanistic studies, CV safety trials, demonstrating safety but also individualisation of treatment targets or understanding the clinical challenges faced when managing special populations, such as those with renal failure, elderly adults, or those fasting as part of Ramadan, real-world studies, and newer HE appraisals in a changing backdrop of regulatory requirements and financial pressures. Vildagliptin was the pioneer of its class, first to be entering an extensive clinical development programme and since then it has been at the forefront of research and development for the class and for the changing diabetes landscape worldwide. ❑

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