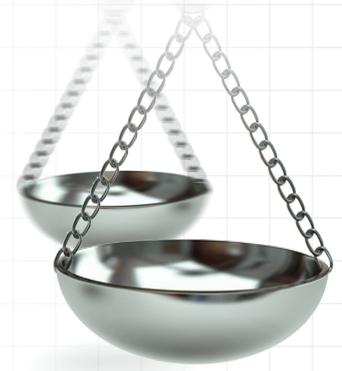




The societal impact of early intensified treatment in patients with Type 2 diabetes mellitus

Journal of **Comparative Effectiveness Research**

Foteini Tsotra^{*,1} , Mathias Kappel², Platon Peristeris¹, Giovanni Bader³, Eva Levi¹, Nicola Lister⁴, Ankur Malhotra⁵ & Dennis A Ostwald^{2,6}

¹WifOR Institute, Athens, Greece

²WifOR Institute, Darmstadt, Germany

³Novartis Pharma AG, Basel, Switzerland

⁴Novartis Global Health & Sustainability, Johannesburg, South Africa

⁵Novartis India Limited, Mumbai, Maharashtra, India

⁶SIBE, Graduate School of the Faculty for Leadership & Management, Steinbeis University, Berlin, Germany

*Author for correspondence: Tel.: +49 615 150 1550; foteini.tsotra@wifor.com

Aim: The current study estimates the societal impact of early intensified treatment compared with initial monotherapy with subsequent treatment intensification in newly diagnosed adults with Type 2 diabetes mellitus in Mexico. **Methods:** An individual patient-level simulation and a static cohort model were employed to simulate the treatment pathway and the probability of experiencing complications of diabetes. The avoided number of events was translated into avoided productivity losses, which were monetized using wages. **Results:** Patients on early intensified treatment experienced approximately 13,000 fewer complication events over 10 years. This was translated into a societal impact of \$54 million (USD). **Conclusion:** Early treatment intensification is likely to be of particular benefit to health outcomes and productivity losses.

First draft submitted: 13 June 2022; Accepted for publication: 9 September 2022; Published online: 28 September 2022

Keywords: antidiabetes treatment • diabetes complications • early intensified treatment • metformin monotherapy • productivity costs • societal impact • Type 2 diabetes mellitus

Background

Type 2 diabetes mellitus (T2DM) is a major public health problem imposing a serious burden on patients and society, accounting for over 90% of the cases with diabetes mellitus (DM), globally [1,2]. T2DM presents high risk for multi-system macrovascular complications, including coronary artery disease (CAD), myocardial infarction (MI), stroke, congestive heart failure (CHF) and peripheral vascular disorders; and microvascular complications, such as neuropathy, nephropathy and retinopathy. Cardiovascular disease (CVD) is a major cause of mortality and morbidity among people with DM, presenting a higher risk of hospitalization for major CVD events and CVD-associated clinical procedures, as compared with non-diabetic individuals [1,3]. Diabetic foot, due to peripheral vascular disorder or neuropathy, is another DM complication that may lead to amputations. Of note, the comorbidity burden tends to increase in older age groups and in men [1].

The prevalence of T2DM is continuously increasing due to socio-economic, demographic, environmental and genetic factors. T2DM is present in all countries without any distinction with respect to the income of the country [2]. However, the incidence and prevalence of T2DM have increased during the past several decades, most markedly in the world's low- to middle-income countries (LMIC). The prevalence and co-prevalence of comorbidities among patients with T2DM is high with 97.5% of patients presenting with at least one comorbid condition and 88.5% with at least two [1].

Uncontrolled DM results in enormous personal and societal costs in terms of resulting complications, quality of life and healthcare system resources [2]. Important economic burden is associated with DM and its complications to patients and families, and to health systems and national economies through direct medical costs and work

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impairment, wages and impacted daily activities. Major cost drivers are hospital and outpatient care with an important part allocated to the rise in cost for specific treatment of diabetes [4].

The global annual cost of diabetes in 2016, including the cost of treating and managing the disease and its complications, was \$825 billion (USD) internationally [5]. The global costs of DM and its consequences are expected to further increase as a share of global gross domestic product (GDP), from 1.8% in 2015 to 2.2% in 2030 [6]. The global burden in the economy attributable to DM, will not decrease, even if countries meet international targets. Thus, drastic measures need to be taken to eliminate the detrimental impact of DM [6].

With regard to Mexico, the total cost for DM has been reported at \$1.2 billion in 2006. The indirect costs were estimated at \$177.2 million. From the indirect costs, individuals with permanent disability contribute to the majority of the costs (\$166.7 million), followed by the mortality cost (\$8 million), and the cost attributed to non-permanently disabled patients (\$2.5 million). The costs of associated complications significantly increase total diabetes costs by 75% in patients with nephropathy, 13% in patients with vascular complications, 3% in patients with neuropathy and 8% in patients with retinopathy [7].

In order to reduce the cost associated with complications, several treatments for T2DM aiming at different metabolic targets and pathways are currently available. The choice of treatment should be informed by a patient-centric approach. Factors such as cardiovascular and kidney comorbidities, hypoglycemia and other side effects, costs, glycemic control and personal preferences should be considered [8,9].

According to the recommendations by the American Diabetes Association (ADA) for the pharmacologic therapy for T2DM, metformin is the preferred first line therapy which should be maintained provided that is well-tolerated and not contraindicated. Treatment with metformin may be supplemented with other agents such as sulfonylureas (SUs), dipeptidyl peptidase-4 (DPP-4) inhibitors, sodium-glucose co-transporter-2 (SGLT-2) inhibitors, glucagon-like peptide 1 (GLP-1) receptor agonists, or insulin, depending on the patient's profile, existing comorbidities, risk factors and therapeutic goals [8].

Early intensified treatment, instead of metformin monotherapy, has been previously shown to decrease the risk of T2DM complications. The UK Prospective Diabetes Study (UKPDS), a large study that ran for 10 years, demonstrated considerably decreased risk of microvascular complications in T2DM patients receiving early intensified treatment with either SUs or insulin [10]. During ten years of post-trial follow-up, the improvements in diabetes outcomes that had been observed, were sustained [11]. Also, the Latin American Diabetes Association, including medical associations of 17 Latin American countries and Mexico, in its consensus statement for the management of hyperglycemia, recognizes the importance of early and intensive blood glucose control on microvascular complication rates [12], as it has been shown by the UKPDS studies [10].

Thus, early combination therapy can be considered at treatment initiation as an option to extend the time to treatment failure. This was demonstrated by the VERIFY (Vildagliptin Efficacy in combination with metformin In For early treatment of type II diabetes) trial, where initial combination therapy was superior to sequential addition of medications for extending primary and secondary treatment failure. Therefore, a greater proportion of patients starting with early intensified treatment achieve the glycemic target [13].

Objectives

The aim of the study was to assess the health and socio-economic implications associated with early intensified treatment in Mexico using an individual patient-level simulation, a population model and a socio-economic evaluation, over a period of 10 years. In the rise of evidence of the impact of T2DM treatment optimization on extended time to treatment failure and possible reduction of the incidence of T2DM complications, it might be yet unclear whether early treatment intensification yields societal economic benefits. Thus, this study estimated the possible avoided productivity losses in terms of paid and unpaid work due to early intensified antidiabetes treatment compared with metformin monotherapy in newly diagnosed T2DM patients in Mexico. The purpose of the study is the monetization of the associated paid and unpaid productivity outcomes, to derive the socio-economic consequences, defined as societal impact of the assessed treatment approach, using Mexico as an exemplar LMIC.

Methods

To quantify the health and socio-economic benefits of early intensified treatment we considered two consecutive valuation steps, the health and the socio-economic valuation. To depict the health outcomes, we implemented a survival analysis, an individual patient-level simulation and a population model. Building on the health outcomes,

a socio-economic evaluation was performed. As a result, we estimated the societal impact of early intensified antidiabetes treatment in Mexico. The model was built in Excel 365.

Patient pathway

This analysis was primarily based on the VERIFY clinical trial [13] due to the unique nature of the study in comparing standard treatment guidelines to early intensification. We assessed the long-term effects of antidiabetes treatment under two treatment scenarios. The first treatment scenario was the stepwise approach after a T2DM diagnosis. This approach was defined as initial therapy with metformin plus placebo and sequential intensification with potent selective inhibitor of DPP-4 vildagliptin if treatment target was not maintained (first treatment failure). Treatment failure is defined as loss of glycemic control, i.e., not maintaining HbA1c levels below 7%. The threshold of 7% was selected due to its clinical relevance to the VERIFY clinical trial [13] and to maintain consistency with glycemic treatment targets in the current guidelines [14]. In the second scenario, patients received early combination treatment, defined as metformin plus vildagliptin until the event of a first treatment failure, and remained on the same treatment strategy until a second treatment failure. In both scenarios, patients were assumed to receive either SUs or insulin after a second treatment failure until the end of the time horizon or until a death event occurs. Insulin and SUs were selected due to their relevance to treatment patterns in Latin America. Due to lack of country-specific data we formed a working hypothesis that once patients had a second treatment failure, 40% receive insulin and 60% SUs.

The treatment pathway chosen for both treatment scenarios is in accordance with the VERIFY trial [13]. The primary end point of the VERIFY, was the time to first treatment failure defined as having HbA1c levels below 7% at two successive visits. The second treatment failure represents the progression (not maintaining glycemic targets) of HbA1c levels after experiencing a first treatment failure.

Health outcomes evaluation

Parametric survival analysis was conducted to model the time to first and second treatment failure over time based on patient-level data from the VERIFY study [15]. The aim of the statistical model was to extrapolate the observed time to treatment failure beyond the study's time horizon and to derive the transition probabilities of having a treatment failure which informed the individual patient-level simulation. We assessed five standard statistical distributions (exponential, Weibull, log-logistic, log-normal and Gompertz) to parametrize the Kaplan–Meier curves. The selection of these distributions was based on current recommendations [16]. We evaluated these parametric models according to their statistical performance. Specifically, we evaluated the goodness-of-fit (i.e., best fit to the observed survival data) visually and by using the Akaike information criterion (AIC) and the Bayesian information criterion (BIC). The model that exhibits the lowest AIC and BIC was chosen as the best fit [16,17]. As a result, we were first able to identify the most suitable parametric model for extrapolating the observed survival data, and thus to derive a full time-to-event curve [18]. Secondly, and based on the fitted parametric distributions, we obtained transition probabilities for the patient simulation model.

By visual inspection, all models in the early intensified treatment group for the time to first treatment failure seemed to have goodness of fit. The least appropriate distribution was the exponential. Similarly, for the second treatment failure, only the exponential distribution did not fit the data well. In the stepwise approach, for the first treatment failure, all distributions were suitable for the data. In contrast, for the second treatment failure, the graphical assessment indicated only the exponential distribution as not appropriate to the observed data. Based on the respective AIC and BIC of the competing distributions, the log-normal distribution was selected to be the best fit for first and second treatment failure in both treatment scenarios ([Supplementary Figures 1 & 2](#)).

For the individual patient-level simulation, a model was constructed with three treatment dependent health states and one death state. The process allowed us to compare the probability of experiencing micro- and macro-vascular complication events at an individual level before extrapolating to a population level. The treatment pathway for each intervention has been described above. The model's time horizon was set at 10 years with a cycle length of 6 months, to ensure capturing potential treatment effects over a relatively long period of time.

Each treatment state includes the probability of experiencing complication events; that is stroke, MI, heart failure (HF), neuropathy and nephropathy ([Figure 1](#)). HF includes HF, chronic HF and CHF. Nephropathy refers to diabetic nephropathy and neuropathy to diabetic neuropathy. The probabilities of experiencing complications while in the no treatment failure and first treatment failure-state were derived from patient-level data of the VERIFY trial for each treatment scenario [15]. We used patient-level data to calculate the number of events as

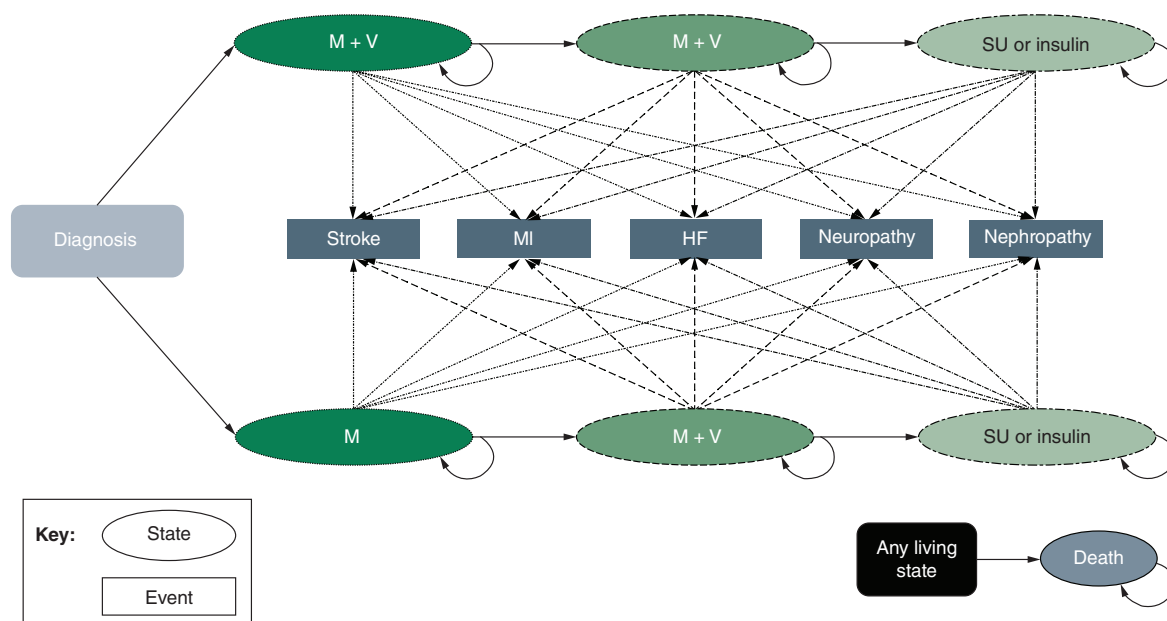


Figure 1. Representation of the individual level simulation model. Each state is a treatment dependent health state. Patients diagnosed with T2DM may receive early combination therapy (M+V) or monotherapy (M). Patients in both treatment arms, could experience a first treatment failure and receive the combination therapy. To note, patients who receive early intensified treatment and experience a treatment failure continue to receive the same therapy (i.e., M+V). If patients experience a second treatment failure, they receive insulin or SUs. From each treatment related state patients may experience complication events or die. HF: Heart failure; M: Metformin; MI: Myocardial infarction; M+V: Metformin + vildagliptin; SU: Sulfonylureas; T2DM: Type 2 diabetes mellitus.

the composite outcome reported in the VERIFY trial [13] and included CVD death, non-fatal stroke and MI, hospitalization for HF, and did not distinguish the number of events occurred among the treatment options. This means that the reported number of events also include the period in which patients were treated with insulin. The probabilities of complications after the second treatment failure, while on insulin or SU treatment, were obtained from reported incidence in a real-world study [19]. We converted the reported incidence into probabilities, to reflect the model's cycle length as per Briggs *et al.* recommendation [20]. The corresponding six-month transition probabilities of experiencing an event are available in [Supplementary Table S1](#). A diabetes-adjusted mortality probability was applied in all treatment states. The overall mortality was derived from Mexican life tables published by the WHO [21]. We accounted for the differential mortality hazard for those with a T2DM diagnosis compared with those without a diagnosis, by assuming a relative risk of 1.85 [22]. Further, we applied a half-cycle correction to account for the fact that transition and events could occur at any point within the cycle.

The model was constructed to evaluate the number of events that occurred in each treatment scenario over the model's time horizon. Thus, the incremental difference in number of events per patient between the two treatment scenarios, constitutes the outcome of the individual patient-level simulation.

To extrapolate the results of the individual patient-level simulation to a population level, we built a static cohort model. This allowed us to quantify the health and thus, societal effects of receiving early intensified antidiabetes treatment. To estimate the cohort size, we used the overall country-specific prevalence in Mexico for the year 2021 for DM [23]. Evidence suggests that T2DM accounts for 90% of all diabetes cases [2]. Consequently, this percentage was applied to the overall country-specific prevalence. It is well documented that diabetes may remain undiagnosed or untreated even in high income countries [24], however, this aspect is particularly relevant in LMICs [24]. To account for this, data of diagnosed patients also treated with any antidiabetes therapy, were also derived from the literature as 52.5% [23] and 80% [25], respectively. By the time the study was conducted no comprehensive country-specific data were available therefore, a hypothetical cohort of 10% receiving early intensified antidiabetes treatment in Mexico is utilized. Consequently, the aforementioned percentages were applied to the overall population.

Further, in compliance with the VERIFY [13] study, we refer to all ages between 20 and 69 years. The static cohort model considers age- and gender-specific subgroups. More precisely, the age groups 20–29, 30–39, 40–49, 50–59 and 60–69 years were evaluated due to their socio-economic relevance. To estimate the proportional size of each sub-cohort within the population of interest, we referred to the patient characteristics in VERIFY, applied the mean age and gender distribution within the VERIFY study population and assumed that age and gender is normally distributed in the previously defined Mexican population of interest [13]. By simulating the static cohort model, we assume that all patients start at the same age in each age group (for example, for the group 20–29 years the starting age is 20 years). We derived the proportional size of each sub-cohort from the VERIFY study to better align with the overall data used in this study (i.e., probability of complications events).

Societal impact evaluation

As a second step of our analysis, we calculated the societal impact by considering both paid and unpaid work activities. Hereby, the overarching question is to what extent individuals contribute to the wealth of an economy and how this contribution might be negatively affected by productivity and activity impairments due to poor health. The societal impact is broadly defined as the incremental difference in avoided paid and unpaid productivity losses associated with health gains as depicted by the number of avoided complication events. Methodologically, paid work productivity losses (productivity impairment) were estimated using the human-capital approach (HCA). The HCA considers human beings as assets and values poor health leading to work impairment as lost production to an economy [26,27]. Based on the simulated health outcomes, i.e., incremental difference in micro- and macro-vascular complication events, we evaluated the avoided productivity losses by drawing correlations between the number of avoided events and productivity and activity impairment. In our analysis we included four complication-specific productivity and activity dimensions; absenteeism, presenteeism, reduced labour force participation after complication events due to no return to work and activity restriction [28–35]. The term activity restriction describes the impairment related to unpaid work activities. The productivity losses related to a disease may influence a country's macroeconomic performance [36]. To capture the losses due to poor health in the Mexican economy, we first determined the working patterns of an average Mexican employee. To do so, we used age- and gender-specific employment rates and working hours derived from the Mexican National Statistical Office (INEGI) [37]. To quantify the loss in active time (unpaid activities), we used data from the Mexican household survey [38]. Unpaid work activities are defined according to the third-person criterion [39]. In other words, unpaid activities that could be replaced by another person are included in our analysis. We assume that T2DM patients do not differ from the general population regarding employment rates, working hours and hours spend in unpaid activities. To monetize the estimated output loss for paid work and unpaid activities due to diabetic complication events, we referred to the generalist approach and thus, applied the average wage and the average minimum wage in Mexico in 2020 in USD [40]. Details on the inputs used and calculation steps are provided in the [Supplementary Tables S1 & S2](#).

Sensitivity analysis

The robustness of the model was assessed with a one-way deterministic sensitivity analysis (DSA) and a probabilistic sensitivity analysis (PSA). A DSA was performed to identify the most influential socio-economic parameters, by varying each selected parameter separately to its lower and upper bound. When reported, parameter uncertainty ranges of $\pm 95\%$ confidence intervals (CIs) were used as lower and upper bound. Otherwise, a standard error (SE) of $\pm 10\%$ of the base-case value was assumed to calculate the lower and upper bound [41]. A PSA was implemented in relation to the uncertainty in clinical input parameters used to examine the health outcomes. The distributions chosen for each input and the relevant distribution parameter calculation were based on Briggs *et al.* recommendations [20]. In case where no data was available for SE, we assumed a conventional SE of 10% [41]. Details on the parameter assessed for uncertainty and distributions are listed in [Supplementary Tables S3 & S4](#).

Results

Population & health outcomes

The modelled patient population amounts to 505,798 patients ([Figure 2](#)). In accordance with the gender distribution reported in the VERIFY study, approximately 55% of the modelled patient population were women ($n = 276,166$) and 45% ($n = 229,632$) men. Most of these patients were in the age group of 50–59 years. Thirty-six percent of the total female patient sub-population and 30% for the total male sub-population were in the combined age groups of 40–49 and 50–59 years, whereas only 0.37% constituted the patient sub-population in the age group of 20–29

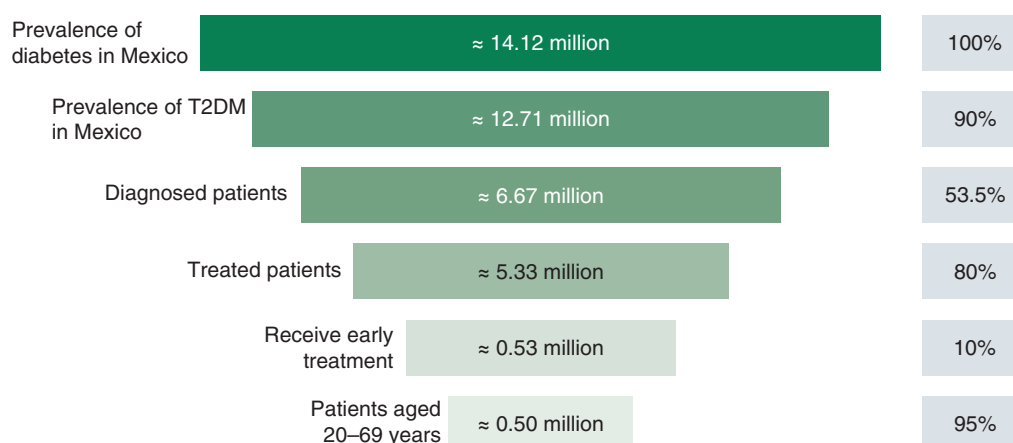


Figure 2. Definition and calculation steps of the patient population.
T2DM: Type II diabetes mellitus.

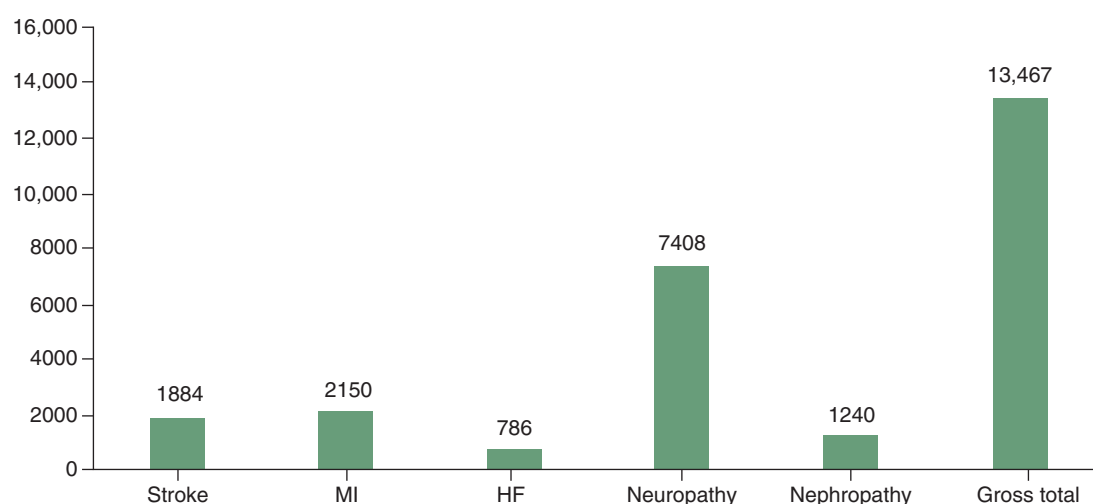


Figure 3. Avoided complication events with early intensified antidiabetes treatment over the treatment course. The total number of avoided events is 13,467. Neuropathy accounts for approximately 55% of avoided events followed by MI and stroke.
HF: Heart failure; MI: Myocardial infarction.

years. More information regarding the age and gender distribution of the modelled patient population is available in [Supplementary Table S5](#). Over a period of 10 years, the simulated patient cohort reduced in size by 13%, to 440,095 patients.

The share of an average patient in the no treatment failure state is comparatively higher in the early intensified treatment group. In contrast, the share of an average patient in first and second treatment failure treatment state is comparatively higher in the comparator group. This implies that patients in the group with early intensified antidiabetes treatment stay comparatively longer in the no treatment failure state, whereas patients in the comparator group with delayed intensified antidiabetes treatment experience faster a first and second treatment failure. The accumulated probability of complication events was lower for the early intensified treatment group over the 10-year treatment course. As shown in [Figure 3](#), over a time horizon of 10 years, an early intensified antidiabetes treatment regimen results in a total of 13,467 avoided complication events. Among the different types of complication events, neuropathy accounts for 55% ($n = 7408$) of avoided events, followed by MI ($n = 2150$) and stroke ($n = 1884$) accounting for 16% and 14% of avoided events, respectively. Nephropathy ($n = 1240$) and HF ($n = 786$) make up 9% and 5%, respectively. We report the number of events occurred per treatment strategy during the 10 year time horizon in [Supplementary Table S6](#).

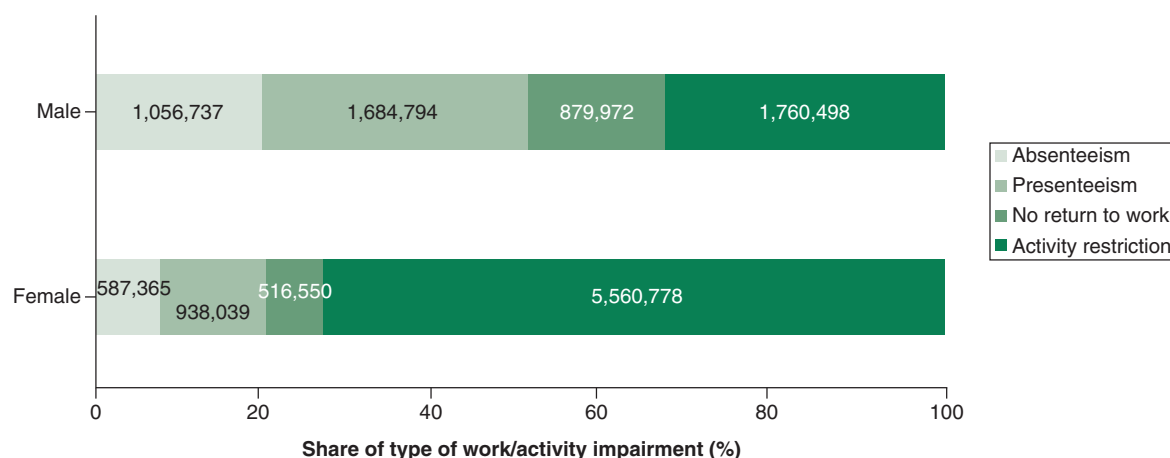


Figure 4. Avoided productivity and activity losses. Avoided losses of unpaid work is higher for females compared with males. Conversely, avoided loss of paid work is higher for males. The observed difference between the two genders is attributed to the employment rates, the working hours and the hours spent in unpaid activities in Mexico.

Table 1. The societal impact of early intensified treatment.

	Paid work (USD)	Unpaid work (USD)
Males	\$28,421,256	\$2,183,018
Females	\$16,025,088	\$6,895,365
Total	\$44,446,344	\$9,078,382

Societal impact

The avoided number of complication events due to early intensified antidiabetes treatment, for both genders, is translated into approximately 13 million avoided hours lost for both paid work and unpaid activities over 10 years. Female patients accounted for 59% (7.6 million) of the total avoided hours lost and men for 41% (5.4 million). This is attributed to the higher female share in our model. For female patients, 27% of the working time losses were attributable to paid work, whereas 73% were attributable to unpaid activities, while for male patients the values were 67% and 33%, respectively. [Figure 4](#) depicts in detail the gender-specific avoided losses in paid productivity and unpaid activities. In male patients, 20% of the quantified paid time loss evolved due to absenteeism, 31% due to presenteeism; an additional 16% was made up by patients not returning to work after a complication event and 33% for activity restrictions (unpaid work productivity). In female patients, absenteeism, presenteeism and lost labor force due to no return to work contributed to 8%, 12% and 7% of paid productivity losses, respectively, whereas the major share was due to activity restriction (73%).

The monetized avoided losses for both paid productivity and unpaid activity reflect the societal impact of early intensified antidiabetes treatment in Mexico and amounted to approximately \$53.5 million over 10 years. [Figure 5](#) & [Table 1](#) show the gender-specific societal impact by paid and unpaid productivity. Moreover, we report the avoided productivity losses per complication and per event for the respective period in [Supplementary Table S7](#).

Sensitivity analysis

The results of the DSA showed that the parameters against which the model is most sensitive is the number of patients on early intensified antidiabetes treatment, the number of weekly working hours, and the rate of presenteeism related to neuropathy, when varying them $\pm 10\%$. [Supplementary Table S8](#) reports the societal impact variation, subject to parameters uncertainty as indicated by the DSA. The model seems to be robust to the clinical inputs assessed in the PSA. After 10,000 model iterations the mean avoided number of events was found to be 13,227 (standard deviation [SD] ± 2391 events), while the mean societal impact was \$52.8 million (SD $\pm$ \$10 million). Results from the sensitivity analyses are also reported [Figure 6](#).

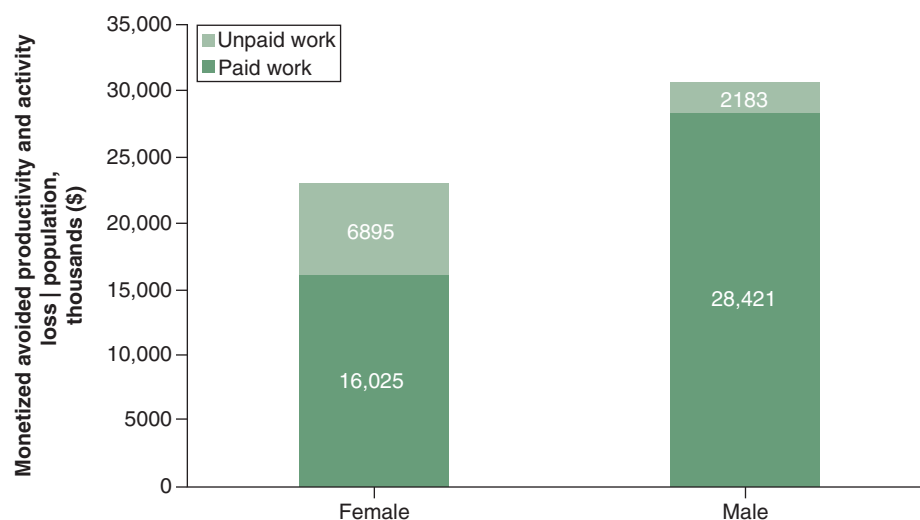


Figure 5. The societal impact per gender by paid and unpaid work of early intensified treatment (in millions). We valued the paid and unpaid activities according to the average (\$7.85 [USD]) and minimum wage (\$1.24 [USD]). Since the avoided loss of unpaid work is higher for females, this leads to a lower societal impact.

Discussion

Poor glycemic control places patients at increased risk of experiencing T2DM complications including micro- and macro-vascular events. Therefore, it is of crucial importance to implement new treatment strategies, such as early and intensified antidiabetes treatment to slow the progression of T2DM in terms of treatment failure and diabetes-related complications. Recent evidence suggests that early treatment intensification in T2DM may lead to improved maintenance of glycemic control compared with the stepwise approach, which consists of metformin monotherapy and sequential intensification after a treatment failure [42]. Additionally, clinical trials have investigated the potential effects of early intensified treatment on micro- and macro-vascular T2DM complications. The ADDITION-Europe trial evaluated the incidence of cardiovascular complications by comparing early intensified treatment to the standard of care. The findings showed minor and non-statistically significant results on cardiovascular risk reduction [43]. The UKPDS 33 trial, also investigated the effect of early intensified treatment with insulin or SUs on diabetes complications. The findings suggested substantial microvascular risk reduction but no significant effects on macrovascular complications [10]. A post-trial monitoring of the same study indicated reduced rate of MI along with maintained microvascular risk reduction in patients starting intensified treatment at diagnosis [11]. Despite the potential benefits of early intensified treatment, there is an ongoing debate on adopting this specific treatment strategy in early stages of T2DM. Major barriers include fear of severe adverse events such as hypoglycemia, clinical inertia and drug acquisition costs [44].

Our analysis was primarily based on the VERIFY which was the first comprehensive attempt to compare early versus late intensified treatment. In accordance with the VERIFY trial [13], we used the example of metformin plus vildagliptin to showcase the effects of early intensified treatment. The present study represents the first thorough attempt to evaluate the societal impact of early intensified treatment in T2DM patients, using Mexico as an exemplar LMIC. To the authors' best knowledge, no similar study exists in the literature. We evaluated metformin combination therapy with a DPP-4 inhibitor, vildagliptin, as an early and intensified treatment option compared with a stepwise approach, starting with metformin monotherapy followed by sequential combination with vildagliptin. Hence, the model applied in this study was not intended to reflect the clinical disease progression of diabetes in T2DM patients but to quantify the difference in two altering treatment scenarios. Our findings are mainly driven by the fact that patients on the stepwise treatment approach experience comparatively faster first and second treatment failure and therefore move faster towards insulin and SUs. Thus, they receive these treatments for a longer period versus the early intensified treatment patients. The calculations suggest that early combination strategy reduces the probability of having a first and a second treatment failure. We estimated that approximately 13,467 complication events could have been avoided within 10 years, leading to a cumulative societal impact of approximately \$54 million. From the 13 million avoided productivity loss hours, 56% and 44% are attributed

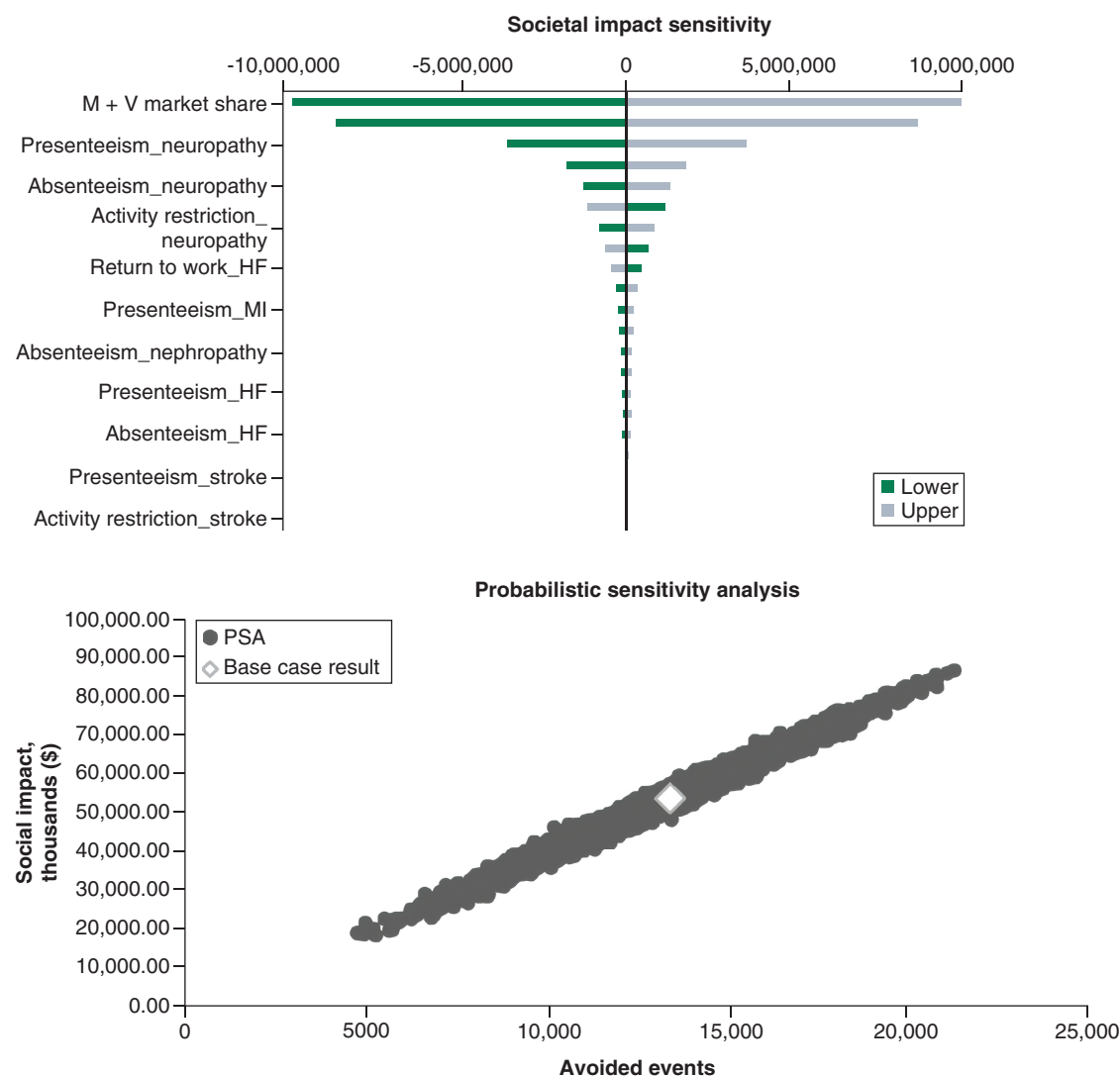


Figure 6. Deterministic and probabilistic sensitivity analysis. In the societal impact sensitivity, each bar represents the change in the societal impact when each parameter reported on the left side changes to its lower and upper bound. In the PSA, each point represents the result of 10,000 model iterations. HF: Heart failure; M+V: Metformin + vildagliptin, MI: Myocardial infarction, PSA: Probabilistic sensitivity analysis.

to unpaid and paid activities, respectively. Female patients accumulate more unpaid avoided working hours lost compared with paid work (73% vs 27%). Conversely, in male patients, a higher percentage of the quantified avoided time loss evolves from paid working hours (67% vs 33%). This gender-specific working pattern is explained by the Mexican employment rates and the working and activity weekly hours spend per gender. Men have higher employment rates and weekly working hours as opposed to women. On the contrary, women are more intensively involved in unpaid work activities than men (i.e., household activities). This highlights that women invest more hours in unpaid activities compared with men. Conversely, men invest more time in paid work. Further, as we applied the minimum wage to unpaid activities and the average wage to paid activities, women have a comparatively lower societal impact compared with men.

Although our findings cannot be directly compared with available evidence from the literature, the VERIFY trial also reported clinical benefits from early intensified treatment regarding macrovascular events. The authors reported that over a period of five years, only 24 patients treated with early intensified treatment experienced macrovascular events as opposed to 33 in the stepwise approach [13]. Moreover, earlier evidence has also suggested the positive effects of improved glycemic control on the incidence of microvascular complications. As mentioned previously,

the UKPDS 33 showed a statistically significant ($p = 0.0099$) risk reduction in microvascular end points of about 25% with intensive blood glucose control compared with conventional treatment. Additionally, the risk reduction of MI was 16% with borderline statistical significance ($p = 0.052$) [10].

The PSA indicated a robust model, as the results were comparable to the base case results. However, the DSA demonstrated three model inputs against which the model is sensitive, namely the hypothetical cohort expected to receive early intensified treatment, the number of weekly working hours and the rate of presenteeism related to neuropathy.

The assessment of the societal impact of an alternative rather than the current treatment approach, provides a wider economic consideration compared with the evaluation of healthcare costs that is usually performed in health technology assessment (HTA) processes. The analysis of productivity gains due to an innovation may also be translated into advancement in the overall population health, as the ability of participating in paid and unpaid activities is associated with improved quality of life and reduced health impairment due to the disease and its complications. The consideration of the unpaid work suggests that this specific dimension is a non-negligible aspect when evaluating economy and costs for the society. Future similar analysis should also consider the effects of impaired health on unpaid activities, as an individual contribution to society is not limited to labor force production. However, as already stated in a previous similar evaluation [45], an important precondition is the robust data collection of unpaid activities in a similar manner to labor work. The aim of the societal impact analysis is to assist decision makers to establish more efficient budget allocation in high impact areas. With this study, we aim to provide evidence of the societal and economic impact of early intensified treatment in treatment naive patients, and we provide a broader picture of pharmaceutical interventions targeting multiple stakeholders and decision makers.

While this study is based on clinical evidence and comprehensive socio-economic data, the methodology presented is subject to several assumptions and limitations. The model reflects a specific treatment pathway instead of clinical progression of the disease, as it is commonly performed in health economic evaluations. We assume 10% of diagnosed and treated T2DM patients aged between 20 and 70 years to receive early intensified treatment. The 10% represents a hypothetical cohort and this age range was chosen due to the age structure in the VERIFY study and the economic importance of these age groups. A more robust model would include the actual percentage of patients receiving early intensified treatment; however, no country-specific data were available. Furthermore, even though the model accounts for the ageing effect and assumes several age groups starting antidiabetes treatment, our results are not generalizable to young people below 20 years and older people above 70 years of age. As mentioned in the methods section, we assume that after a second treatment failure, 60% of patients were treated with SUs and 40% with insulin. In real-world settings, more antidiabetes treatment options might be available, such as SGLT-2 inhibitors or GLP-1 agonists. However, the market shares of these therapies are relatively low in LMICs and thus, play a minor role in available treatment options. Further, clinical trials testing the efficacy of those agents are more likely to consider a different patient population compared with the VERIFY study [46–52], such as, patients with progressed T2DM and established CVDs or those at a high risk of CVD rather than newly diagnosed patients. Hence, in this study we examined a conservative scenario where patients can be treated with insulin (40%) or SUs (60%) after second treatment failure due to scarcity of country-specific data. In addition, we assumed constant complication event probabilities throughout the study time horizon. This conservative approach may lead to an underestimation of the impact of early intensified treatment as the probability of experiencing a complication event naturally decreases with treatment response and in turn, increases with disease progression. However, time dependent data on the occurrence of complication events per treatment scenario and per treatment-related health state were not available. Moreover, to quantify complication event probabilities while on insulin and SUs, we used evidence from a small sample size real-world study. This may have introduced inaccuracies into the model. Our initial objective was to find high quality clinical trials, comparable to the VERIFY, reporting the incidence of micro- and macro-vascular complication while on insulin and SUs, thus we conducted an extensive literature review. To the best of our knowledge, the majority of current literature investigating the incidence of micro- and macro-vascular complications concerns treatments such as SGLT-2 inhibitors and GLP-1 receptor agonists, which were not included as treatment strategies in our model, due to their low market shares in the target setting. This observational study was the only one identified that included both treatments of interest and all vascular events that were assessed in our model.

We used the overall country prevalence in Mexico to populate our model. Primarily, we only had data on the diagnosed and treated patients of the prevalent population, aspects that we considered to be of particular importance in T2DM and especially in a developing country. Additionally, the incident population, may remain untreated

for a period that will implicitly allow us to consider them as prevalent population. This is of notable importance since this research concerns early treatment intensification. Therefore, using prevalence seemed more reasonable. By following this approach, we applied the same method as Abushanab *et al.* [53]. However, we acknowledge that this approach approximates the number of patients. Therefore, our population estimate presents a more hypothetical cohort and does not necessarily reflect the real-world situation.

Due to scarcity of studies, some productivity input data were derived from studies outside Mexico. For example, absenteeism, presenteeism and activity restriction rates for HF were obtained from a study conducted in the USA [32]. Our objective was to select high-quality studies that considered the Mexican population, and therefore, we performed an extensive literature search to identify relevant evidence. However, the evidence was scarce; therefore, we were obligated to expand our literature search to other countries. First, we focused on data collected from Latin American countries preferably. We were able to identify only a few studies for Latin America (i.e., Brazil). Thus, our search expanded to other low- to middle-income countries which again did not yield appropriate results. We thus performed a non-country-specific search which also led to few selected articles. The publications selected met the following criteria: included the productivity parameters pertained to the specific (or similar) diabetes events evaluated in this project; reported all or most of the productivity parameters of interest; and most recent publications. Two studies [54,55] assessed the days absent from work due to diabetes complications in Sweden and Denmark. However, these two studies did not assess presenteeism and activity restriction. Thus, and in relation to the second point of our selection strategy, the current study did not include their findings as productivity impairment parameters. Every input parameter may be subject to uncertainty. The effect of uncertainty around the productivity parameters was assessed in the DSA by varying them to their lower and upper bound. Return to work after a MI is associated with moderate-to-low uncertainty. The base case value for this input was chosen from a study conducted in Cuba. Although we acknowledge that Cuba and Mexico have substantially different social and healthcare system and Cuba might not necessarily reflect the treatment situation in Mexico, this study was chosen as the most appropriate. Most of the identified studies concerned high income countries, such as Germany [56], Spain [57] and USA [58]. Further, we were able to identify two studies from Iran assessing this parameter of interest [59,60] and one from China [61]. However, choosing Cuba as a proxy country for Mexico was deemed more appropriate as despite the obvious differences, Cuba is an upper middle-income country in Latin America. Thus, people living in Cuba are more likely to share similar characteristics with Mexicans that will eventually affect health outcomes, e.g., diet, compared with people from Iran and China. The base case value of return to work after a HF was selected from a study conducted in Denmark, as this was the only identified study. Similarly, we acknowledge that the estimate from Denmark may not necessarily reflect the situation in Mexico. However, as indicated by the DSA, our societal impact estimate was not particularly sensitive to this parameter. For stroke, we used evidence from Portugal [29]. This study was part of a European study including 7 countries, most of them having an advanced and better structured healthcare system [62]. In future, further research could potentially investigate the productivity losses (absenteeism, presenteeism and activity restriction) associated with vascular diabetes complications in Mexico. The study used for HF [32] estimated the productivity losses for CHF. We assume that there are no differences in productivity and activity impairment for those suffering from HF, CHF and chronic HF. For productivity impairment due to neuropathy, we chose a study from Brazil, as this Latin America country has most likely similar healthcare and social system to Mexico. This study reports productivity and activity impairment due to neuropathic pain. However, the cause of neuropathic pain is broadly defined [35]. This may be a broader definition of neuropathy compared with VERIFY study [13] and consequently in our model. Nevertheless, due to limited data availability, we chose the best available evidence for measuring productivity losses. Finally, for nephropathy we selected a study from the USA for consistency reasons, as it was the only study available reporting all the parameters of interest [34]. Additionally, to the best of our knowledge, studies trying to assess productivity impairment due to kidney disease are likely to include patients who have progressed disease, for example end stage renal disease (ESRD). Further details regarding the productivity and activity inputs used can be found in [Supplementary Table S2](#).

We assume that the T2DM patient population does not diverge from the average Mexican population in terms of their work behavior, i.e., labor force participation rate and number of hours worked. To the best of our knowledge, there is no employment data available to differentiate T2DM patients from the general population in Mexico. Moreover, productivity and activity related costs were considered for a period of 6 months (per cycle). However, impairments due to complication events usually affect patients for a longer period than 6 months, leading to higher socio-economic costs. In this regard, the societal impact may also be underestimated. Finally, the data from the VERIFY study were collected from eligible participants across 34 countries. Precisely, 52.4% of the patient

population are from Europe, 26.8% Latin Americans, 17.2% Asians, 3.1% South Africans and 0.5% Australians [63]. As the VERIFY study was a multinational clinical trial, it defines a broad population and the transferability of the findings, although slightly impaired, it is sensible. However, the multinational nature of the clinical trial and the fact that a great percentage of participants in the VERIFY study came from Latin American countries, including Mexico, make our extrapolation reasonably applicable to the target country population. Additionally, the VERIFY clinical trial is the first study to provide robust evidence of the effects of early intensified treatment. To the best of our knowledge, no other study exists at a country level (nor at a global level), providing such evidence. Although the international nature of the trial allows us to assume generalizability and transferability of the findings to LMICs – particularly considering the under-representation of the developing world in global clinical trial platforms [64], the authors acknowledge that factors associated with ethnicity, diet, environment, educational level, level of diabetes awareness, and other regional variations may significantly influence the progression of diabetes in each country.

Conclusion

T2DM is a highly prevalent disease-causing high health and socio-economic burden worldwide. The efficacy of early intensified treatment in terms of delayed time to treatment failure and potentially favorable outcomes of cardiovascular events has already been shown in the VERIFY study. Thus, clinical data appears to support the importance of achieving glycemic control within the first month of diagnosis. Building on that evidence, we measure the societal impact of early intensified treatment adopting a macroeconomic perspective. We aimed to provide a comprehensive evaluation of the socio-economic effects of the introduction of early intensified antidiabetes treatment with vildagliptin plus metformin in Mexico. Our approach considers health as an asset that leads to societal and economic stability. The results of our analysis demonstrate that early intensified treatment is likely to downregulate the overall incidence of diabetes complications leading to potentially improved health outcomes and reduced productivity losses. The demonstrated long-term impact of healthcare interventions in monetary terms may serve as a common measure and basis for decision makers, clinical practitioners, and various relevant stakeholders to appraise patient and economic related outcomes. Building on this, and by factoring long-term consequences of health interventions, comprehensive decisions in resource allocation can be made.

Summary points

- Diabetes may cause significant impairment in patients, and the majority of this impairment is attributed to major complications.
- Clinical evidence suggests the potential benefits of early intensified treatment in Type 2 diabetes mellitus patients.
- The use of early intensified antidiabetes treatment prolongs the time to treatment failure compared with the stepwise approach.
- The use of early intensified antidiabetes treatment is likely to result in a lower incidence of microvascular complication events such as neuropathy and nephropathy compared with the stepwise approach.
- The use of early intensified treatment would potentially decrease the number of macrovascular diabetes-related complication events such as myocardial infarction, stroke and heart failure, compared with the stepwise approach.
- The potential avoided complication events may reduce the productivity and activity impairment associated with diabetes complications measured as avoided paid and unpaid working hours loss.
- It is estimated that the 13,000 avoided complication events translate into 13 million hours of paid and unpaid avoided activity losses.
- Avoided productivity losses were valued using wages, leading to a monetary estimate of \$53.5 million (USD).

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: www.futuremedicine.com/doi/suppl/10.2217/cer-2022-0110

Author contributions

All listed authors have substantially contributed to the creation of this research. F Tsotra and M Kappel were responsible for study conception, design, analysis, literature review, and drafting of the manuscript. P Peristeris was responsible for the literature review, gave substantial input on developing the study concept and drafted the manuscript. E Levi was responsible for the literature review

and for drafting the manuscript. DA Ostwald supervised and gave substantial input on developing the study concept. G Bader, N Lister and A Malhotra supervised and gave substantial input on developing the study concept. All authors were responsible for the interpretation of the data, critical revision of the manuscript for important intellectual content, and approval of the manuscript.

Financial & competing interests disclosure

This work was funded by Novartis Pharma AG. F Tsotra, P Peristeris, E Levi and M Kappel are employees of WifOR institute, an independent economic research institute in Darmstadt. DA Ostwald is the CEO of WifOR institute. G Bader, A Malhotra and N Lister are employees of Novartis. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Data sharing statement

The authors certify that this manuscript reports the secondary analysis of clinical trial data that have been shared with them, and that the use of this shared data is in accordance with the terms agreed upon their receipt. The source of this data is: Novartis Pharma AG/VERIFY study (NCT01528254).

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