Cost-Effectiveness of Once-Weekly Semaglutide versus Empagliflozin in People with Type 2 Diabetes and Inadequate Glycemic Control in Sweden

Authors: M. Löndahl[1], K. Nihlberg[2], Å. Ericsson[2]
[1]Lund University, Department of Clinical Sciences, Lund, Sweden, [2]Novo Nordisk Scandinavia AB, Malmö, Sweden.

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Background and aims

Background

- Once-weekly semaglutide is a glucagon-like peptide (GLP-1) analogue. It was judged as the most cost effective glucagon-like peptide-1 receptor agonist (GLP-1RA) by The Dental and Pharmaceutical Benefits Agency, TLV, and therefore gained reimbursement in Sweden in 2018.[1]
- GLP-1RAs and sodium-glucose cotransporters 2 inhibitors (SLGT-2i) are both antidiabetic agents for treatment of type 2 diabetes (T2D). Both treatment options exert their effectiveness through distinct but different physiologic, metabolic and molecular mechanisms.[2–5] (Figure 1)
- The role of increased HbA1c as a strong association for cardiovascular outcomes highlights the importance to lower HbA1c.[6,7]
- These glucose lowering treatments have been compared from an efficacy perspective, however this is the first assessment of the cost-effectiveness (CEA) of semaglutide vs. empagliflozin from a Swedish societal perspective.[8]

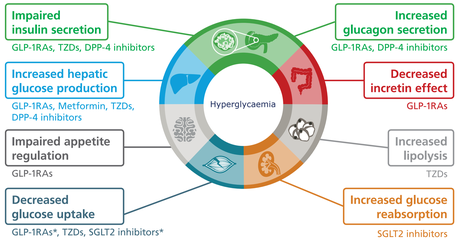
Aim

To estimate the cost-effectiveness of once-weekly semaglutide 1 mg vs. empagliflozin 25 mg in patients with T2D inadequately controlled with metformin monotherapy from a Swedish societal perspective.

Materials and methods

- This cost-effectiveness analysis (CEA) was made using the Institutet för Hälso- och Sjukvårdsekonomi (IHE) Diabetes Cohort Model.[9]
- The model is based on metabolic risk equations from the Swedish National Diabetes Register and UKPDS, and does not regard any plausible cardiovascular benefits in addition to what's already captured through changes in the traditional risk factors (including HbA1c, BMI, lipids, blood pressure, age) in these equations. Treatment effects are applied to the biomarkers (HbA1c, blood pressure, lipids and BMI) and the evolution of biomarkers and hypoglycaemia is simulated annually. The progression of the cohort between different health states is predicted by the risk equations.
- Analyses were conducted from a Swedish societal perspective spanning over 40 years.
- Input data for the analyses on the differences in HbA1c decline and weight reduction between the treatments were obtained from a published network meta-analysis investigating the differences in glycemic control between once-weekly semaglutide and once-daily empagliflozin, where semaglutide reached significantly better improvements in both endpoints.[8] (Table 1)
- Baseline patient characteristics were obtained from the SUSTAIN 7 clinical trial.[10]
- Both treatments result in decreased HbA1c, but due to the progressive nature of the disease HbA1c will eventually increase again and intensification will be needed. Data on this increase (0.14 percent units per year) were taken from the ADOPT study.[11] Treatment intensification was made in two steps – basal insulin and basal-bolus insulin – when HbA1c reached the baseline value. Insulin doses and efficacy of the treatment intensification data were obtained from a published source.[12]
- The cost of pharmaceuticals and self-monitored blood glucose tests (SMBG) were based on the pharmacy selling price (Apotekens utpris, AUP, www.TLV.se) in April 2019. The costs of long-term diabetes-related complications were identified from a literature review made for a published cost-effectiveness analysis, and adjusted to the current price level.[13]
- Baseline values of HbA1c, BMI and age were varied over a number of hypothetical sensitivity analyses to identify cost-effectiveness in different patient groups.

Figure 1: GLP-1RA, SGLT2i and other treatments target different pathophysiologic defects of T2D



Adapted from DeFronzo RA. 2009[5]; 2015[3]; 2017[4] and Ahrén B. 2017[5]
*Indirectly, weight loss enhances both muscle and hepatic sensitivity to insulin. DPP-4, dipeptidyl peptidase-4; GLP-1RA, glucagon-like peptide-1 receptor agonist; SGLT2, sodium glucose co-transporter-2 inhibitor; TZD, thiazolidinedione.

Table 1: Relative treatment effects of semaglutide 1.0 mg vs. empagliflozin 25 mg[8]

	Mean difference and 95% CI
HbA1c (%)	-0.80 (-1.04, -0.58)
HbA1c (mmol/mol)	-8.5 (-11.2, -6.0)
Weight (kg)	-2.05 (-2.94, -1.15)

Results

- Our results shows that semaglutide is a cost-effective treatment option compared to empagliflozin in patients with inadequate control on metformin. (Table 2)
- Semaglutide imposed a higher total cost and more quality-adjusted life-years (QALYs) in all analyses vs. empagliflozin with a cost difference of SEK 3 300–55 700 over a 40-year perspective and a QALY gain of 0.137–0.242.
- Cost per QALY varied from SEK 16 000–407 000, where the lowest cost per QALY was found in patients with higher baseline HbA1c and lower age (Table 2), while baseline BMI did not have any significant impact on the results. A diabetes treatment is valued cost-effective in Sweden if cost per QALY is below SEK 500 000.
- Time to insulin initiation was 13 years for semaglutide and 8 years for empagliflozin, based on the initial HbA1c reduction, which was significantly higher for semaglutide as compared to empagliflozin.[8]
- Our results are largely driven by the reduction in complications due to the HbA1c decline with semaglutide compared to empagliflozin. As an example, the result including a breakdown of costs over 40 years, for the analysis with baseline values: 56 years, HbA1c 60 mmol/mol and BMI 30 is presented in Table 3.

Table 2: Cost/QALY (SEK) depending on baseline HbA1c, age and BMI

		HbA1c			
Age	BMI	55 mmol/mol (7.2%)	60 mmol/mol (7.65%)	65 mmol/mol (8.1%)	70 mmol/mol (8.55%)
56 years	28	224 000	142 000	50 000	16 000
	30	226 000	143 000	52 000	18 000
	34	232 000	148 000	56 000	23 000
66 years	28	389 000	290 000	186 000	156 000
	30	394 000	293 000	188 000	158 000
	34	407 000	302 000	193 000	162 000

(€ 1 = SEK 10.47, 19MAR2019)

Discussion

- This CEA indicates that semaglutide is a cost-effective treatment option vs. empagliflozin in patients with T2D inadequately controlled with OADs from a Swedish societal perspective.
- The results suggest that semaglutide could be initiated early to target optimal HbA1c level. Lowest cost per QALY was found in patients with higher baseline HbA1c and lower age. The reason for this is that the absolute risk for complications is higher at higher HbA1c levels, so even though the incremental difference in HbA1c between treatments is kept constant, the total number of predicted complications is increased.
- Baseline BMI had little impact on the results, indicating that it is equally cost-effective to use either semaglutide or empagliflozin in patients with baseline BMI 28 or 34.
- In this simulation model, initial cost for semaglutide is higher compared to empaglifozin, however the long term costs for microalbumuria, macroalbumuria, end stage renal disease and retinopathy are lower due to more pronounced effect on HbA1c.
- As a standard in CEA, a long-term perspective is used in order to be able to follow patients over their full life span. In T2D, this implies modelling over at least 40 years, as in this analysis. However, the last 20 years of analysis did not affect the overall conclusions.

Table 3: Results, including breakdown of costs (SEK) over 40 years, an example from the analysis with baseline values: 56 years, HbA1c 60 mmol/mol and BMI 30

	Semaglutide 1.0 mg	Empagliflozin 25 mg	Increment
QALYs	8,445	8,226	0,219
Costs			
Anti-Hyperglycaemic Treatment	174 225	97 314	76 911
Hypoglycaemia	2 355	3 032	-677
Dyslipidemia Treatment	24 367	24 287	80
Retinopathy	6 069	8 729	-2 660
Neuropathy	113 949	116 156	-2 206
Nephropathy	83 271	113 310	-30 039
IHD	41 836	42 634	-798
MI	27 874	28 748	-874
Stroke	23 330	23 744	-414
CHF	40 283	41 958	-1 675
Indirect cost	342 985	349 325	-6 340
Total Direct Costs	537 560	499 913	37 647
Total Costs	880 545	849 238	31 307
Cost/QALY			
Health care perspective	-	-	172 020
Societal Perspective	-	-	143 051

(€ 1 = SEK 10.47, 19MAR2019)

Conclusion

Using modelling based on metabolic risk equations, semaglutide was cost-effective in all subgroups analysed, while the lowest cost per QALY was found in patients with higher baseline HbA1c and lower age.

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