**Supplementary materials:**

Table S1: Baseline Characteristics

| Variable | Mean (SD) | Unit | Reference |
| --- | --- | --- | --- |
| **PATIENT DEMOGRAPHICS** |  |  |  |
| Start age | 58 (10) | Years | [[1](#_ENREF_1)] |
| Duration of Diabetes | 7 (6) | Years | [[1](#_ENREF_1)] |
| Prop. Male | 0.506 | [0-1] | [[1](#_ENREF_1)] |
|  |  |  |  |
| **BASELINE RISK FACTORS** |  |  |  |
| HbA1c | 8.14 (0.94) | %-points | [[2](#_ENREF_2)] |
| SBP | 132.15 (14.69) | mmHg | [[2](#_ENREF_2)] |
| DBP | 80.36 (9.01) | mmHg | [[2](#_ENREF_2)] |
| T Chol | 181.51 (41.70) | mg/dl | [[2](#_ENREF_2)] |
| HDL | 45.47 (10.58) | mg/dl | [[2](#_ENREF_2)] |
| LDL | 115.00 | mg/dl | Recalculated using [[3](#_ENREF_3)] |
| TRIG | 103.19 | mg/dl | [[4](#_ENREF_4)] |
| BMI | 32.82 (6.11) | kg/m2 | [[2](#_ENREF_2)] |
| eGFR | 95.00 (15.00) | ml/min/1.73m2 | [[1](#_ENREF_1)] |
| Haemoglobin | 13.85 | gr/dl | [[4](#_ENREF_4)] |
| WBC | 6.90 | 106/ml | [[4](#_ENREF_4)] |
| Heart rate | 72.00 | Bpm | [[5](#_ENREF_5)] |
| WHR | 0.93 |  | [[6](#_ENREF_6)] |
| uAER | 4.50 | mg/mmol | [[4](#_ENREF_4)] |
| Serum Creatinine | 0.88 | mg/dl | [[4](#_ENREF_4)] |
| Serum albumin | 4.75 | g/dl | [[4](#_ENREF_4)] |
| Prop. smoker | 0.15 | [0-1] | [[4](#_ENREF_4)] |
| Cigarettes/day | 3.00 |  | [[7](#_ENREF_7)] |
| Alcohol consumption oz/week | 3.00 | Oz/week | [[8](#_ENREF_8)] |
|  |  |  |  |
| **RACIAL CHARACTERISTICS** |  |  |  |
| Prop. White | 0.6200 | [0-1] | [[1](#_ENREF_1)] |
| Prop. Black | 0.0720 | [0-1] | [[1](#_ENREF_1)] |
| Prop. Hispanic | 0.2420 | [0-1] | [[1](#_ENREF_1)] |
| Prop. Native American | 0.0060 | [0-1] | [[1](#_ENREF_1)] |
| Prop. Asian/Pacific Islander | 0.0600 | [0-1] | [[1](#_ENREF_1)] |
|  |  |  |  |
| **BASELINE CVD COMPLICATIONS** |  |  |  |
| Prop. MI | 0.013 | [0-1] | [[4](#_ENREF_4)] |
| Prop. Angina | 0.005 | [0-1] | [[4](#_ENREF_4)] |
| Prop. PVD | 0.001 | [0-1] | [[4](#_ENREF_4)] |
| Prop. stroke | 0.060 | [0-1] | [[9](#_ENREF_9)] |
| Prop. HF | 0.002 | [0-1] | [[4](#_ENREF_4)] |
| Prop. Atrial fibrillation | 0.013 | [0-1] | [[4](#_ENREF_4)] |
| Prop. LVH | 0.006 | [0-1] | [[4](#_ENREF_4)] |
|  |  |  |  |
| **BASELINE RENAL COMPLICATIONS** |  |  |  |
| Prop. Microalbuminuria | 0.027 | [0-1] | [[4](#_ENREF_4)] |
| Prop. macroalbuminuria | 0.006 | [0-1] | [[4](#_ENREF_4)] |
| Prop. ESRD | 0.00118 | [0-1] | [[4](#_ENREF_4)] |
|  |  |  |  |
| **BASELINE RETINOPATHY COMPLICATIONS** |  |  |  |
| Prop. BDR | 0.047 | [0-1] | [[4](#_ENREF_4)] |
| Prop. PDR | 0.071 | [0-1] | [[10](#_ENREF_10)] |
| Prop. SVL | 0.030 | [0-1] | [[11](#_ENREF_11)] |
|  |  |  |  |
| **BASELINE MACULAR EDEMA** |  |  |  |
| Prop. ME | 0.001 | [0-1] | [[4](#_ENREF_4)] |
|  |  |  |  |
| **BASELINE CATARACT** |  |  |  |
| Prop. cataract | 0.047 | [0-1] | [[4](#_ENREF_4)] |
|  |  |  |  |
| **BASELINE FOOT ULCER COMPLICATIONS** |  |  |  |
| Prop. uninfected ulcer | 0.009 | [0-1] | [[4](#_ENREF_4)] |
| Prop. infected ulcer | 0.000 | [0-1] |  |
| Prop. healed ulcer | 0.000 | [0-1] |  |
| Prop. history of amputation | 0.000 | [0-1] |  |
|  |  |  |  |
| **BASELINE NEUROPATHY** |  |  |  |
| Prop. neuropathy | 0.082 | [0-1] | [[4](#_ENREF_4)] |

SD: Standard deviation; HbA1c: glycated haemoglobin A1c; SBP: systolic blood pressure; DBP: diastolic blood pressure; T Chol: total cholesterol; HDL: high density lipoprotein; LDL: low density lipoprotein; TRIG: triglycerides; BMI: body mass index; eGFR: estimated glomerular filtration rate; WBC: white blood cells; WHR: waist-to-hip ratio; uAER: urinary albumin/creatinine ratio; MI: myocardial infarction; PVD: peripheral vascular disease; HF: heart failure; LVH: left ventricular hypertrophy; ESRD: end-stage renal disease; BDR: background diabetic retinopathy; PDR: proliferative diabetic retinopathy; SVL: severe vision loss; ME: macular edema

Table S2: Treatment Effects – First Line

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | Empagliflozin | SE | Oral semaglutide | SE | Unit | | Source |
| **Treatment Policy estimand** |  |  |  |  |  |  | |
| Change in baseline HbA1c | -0.90 | 0.026 | -1.30 | 0.03 | %-points | [[1](#_ENREF_1)] | |
| SBP change from baseline | -4.34 | 0.63 | -4.85 | 0.65 | mmHg | [[2](#_ENREF_2)] | |
| DBP change from baseline | -2.67 | 0.44 | -2.27 | 0.45 | mmHg | [[2](#_ENREF_2)] | |
| T Chol change from baseline | 4.74 | 1.57 | -5.08 | 1.62 | mg/dl | [[2](#_ENREF_2)] | |
| HDL Chol change from baseline | 3.11 | 0.34 | 0.73 | 0.35 | mg/dl | [[2](#_ENREF_2)] | |
| BMI Change from baseline | -1.29 | 0.03 | -1.36 | 0.03 | kg/m2 | Recalculated\* [[1](#_ENREF_1)] | |
|  |  |  |  |  |  |  | |
| **Trial Product estimand** |  |  |  |  |  |  | |
| Change in baseline HbA1c | -0.79 | 0.05 | -1.30 | 0.05 | %-points | [[2](#_ENREF_2)] | |
| SBP change from baseline | -4.34 | 0.63 | -4.85 | 0.65 | mmHg | [[2](#_ENREF_2)] | |
| DBP change from baseline | -2.67 | 0.44 | -2.27 | 0.45 | mmHg | [[2](#_ENREF_2)] | |
| T Chol change from baseline | 4.74 | 1.57 | -5.08 | 1.62 | mg/dl | [[2](#_ENREF_2)] | |
| HDL Chol change from baseline | 3.11 | 0.34 | 0.73 | 0.35 | mg/dl | [[2](#_ENREF_2)] | |
| BMI Change from baseline | -1.37 | 0.09 | -1.73 | 0.10 | kg/m2 | [[2](#_ENREF_2)] | |
|  |  |  |  |  |  |  | |

SE: Standard error; HbA1c: glycated haemoglobin A1c; SBP: systolic blood pressure; DBP: diastolic blood pressure; T Chol: Total Cholesterol; HDL Chol: High Density Lipoprotein Cholesterol; BMI: Body Mass index

In Rodbard et al [[1](#_ENREF_1)] starting body weight, BMI and absolute decrease in body weight is reported. Based on this the decrease in BMI per arm was calculated.

Table S3: Adverse Events

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Empagliflozin | Oral semaglutide | Unit | Source |
| **Treatment Policy estimand** |  |  |  |  |
| NSHE rate | 9.535 | 10.976 | /100 pt. yrs | Recalculated [[1](#_ENREF_1)] |
| SHE1 rate | 0.244 | 0.244 | /100 pt. yrs | Recalculated [[1](#_ENREF_1)] |
| SHE2 rate | 0 | 0 | /100 pt. yrs | Recalculated [[1](#_ENREF_1)] |
| **Trial product estimand** |  |  |  |  |
| NSHE rate | 1.90 | 2.25 | /100 pt. yrs | [[2](#_ENREF_2)] |
| SHE1 rate | 0.24 | 0.25 | /100 pt. yrs | [[2](#_ENREF_2)] |

NSHE: Non-severe hypoglycaemia rate; SHE1: Severe hypoglycaemia rate (not requiring medical assistance); SHE2: Severe hypoglycaemia rate (requiring medical assistance).

Rodbard et al [[1](#_ENREF_1)] report incidence and we recalculated them to rates per 100 patient years assuming that study duration was 1 year for all patients.

Table S4: Treatment effects for second/third line treatments (treatment policy estimand)

|  |  |  |  |
| --- | --- | --- | --- |
|  | 2nd line Insulin | 3rd line Insulin | Source |
| HbA1c (change from baseline) | -0.5682 | -0.7109 | [[12](#_ENREF_12)] |
| BMI (change versus previous line | 0 | +1.294/1.357\* | Assumption |
| NSHE event rate | 486 | 486 | [[13](#_ENREF_13)] |
| SHE1 event rate (req. non. med. assist.) | 1.76 | 1.76 | [[13](#_ENREF_13)] |
| SHE2 event rate (req. med. assist.) | 0.24 | 0.24 | [[13](#_ENREF_13)] |

HbA1c: glycated haemoglobin A1c; BMI: body mass index; NSHE: non-severe hypoglycaemia event; SHE: severe hypoglycaemia event

\* for empagliflozin and oral semaglutide

Table S5: Proportion of patients on preventive medication

|  |  |  |
| --- | --- | --- |
| Item | Value | Source |
| Prop 1° prevention aspirin | 0.551 | [[14](#_ENREF_14)] |
| Prop 2° prevention aspirin | 0.912 | [[15](#_ENREF_15)] |
| Prop 1° prevention Statins | 0.378 | [[14](#_ENREF_14)] |
| Prop 2° prevention Statins | 0.898 | [[15](#_ENREF_15)] |
| Prop 1° prevention ACEI/ARB | 0.310 | [[14](#_ENREF_14)] |
| Prop 2° prevention ACEI/ARB | 0.840 | [[15](#_ENREF_15)] |

ACEI/ARB: angiotensin-converting enzyme inhibitor/angiotensin-receptor blocker

Table S6: Screening and patient management proportions

|  |  |  |
| --- | --- | --- |
| Item | Value | Source |
| Prop screened eye disease | 0.870 | [[16](#_ENREF_16)],[[17](#_ENREF_17)] |
| Prop screened for renal disease | 0.910 |
| Prop receiving intensive insulin after MI | 1.000 | Assumption |

MI - Myocardial infarction

Table S7: Sensitivity and specificity of tests.

|  |  |  |
| --- | --- | --- |
| Item | Value | Source |
| Sensitivity eye screening | 0.920 | [[18](#_ENREF_18)] |
| Specificity eye screening | 0.960 |
| Sensitivity microalbuminuria screening | 0.830 | [[19](#_ENREF_19)] |
| Sensitivity macroalbuminuria screening | 0.830 |
| Specificity renal screening | 0.960 |

Table S8 Annual treatment costs applied (DKK, AIP 2020, [[20](#_ENREF_20)])

|  |  |
| --- | --- |
| INTERVENTION | Annual Cost (DKK) |
| Empagliflozin | 4,164.70 |
| Oral semaglutide | 9,326.05 |
| Metformin | 84.25 |
| Long-acting insulin 2L 0.7 IU/kg (including administration costs) | 10,036.52 |
| Long-acting insulin 3L 0.9 IU/kg (including administration costs) | 11,447.76 |
| *Administration costs* |  |
| Disposable needles (BD Thin Wall Penkanyle 31G 5mm) | 1,203.33 |
| SMBG testing (FreeStyle Precision) | 3,479.05 |
| SMBG testing (BD Microfine) | 414.81 |

DKK: Danish Krone; AIP: Apotekets Indkøbspris (Pharmacy Purchase Price); SMBG: Self-monitoring of blood Glucose

Table S9 Cost Inputs for the CDM (Costs inflated to 2020 values, DKK)

| Variable | Value | Reference | | |
| --- | --- | --- | --- | --- |
| **Discounting** | | | |
| Clinical discount rate | 4.0% | [[20](#_ENREF_20)] | | |
| Costs discount rate | 4.0% | [[20](#_ENREF_20)] | | |
|  |  |  | | |
| **Management Costs** |  |  | | |
| Annual statins treatment | 61.08 | [[21](#_ENREF_21)], AIP | | |
| Annual Aspirin | 32.14 | [[21](#_ENREF_21)], AIP | | |
| Annual ACE inhibitor/ARB | 58.01 | [[21](#_ENREF_21)], AIP | | |
| Annual screening microalbuminuria | 191.95 | [[20](#_ENREF_20)] | | |
| Annual screening GRP | 191.95 | [[22](#_ENREF_22)] | | |
| Stopping ACE inhibitor due to side effects | 143.44 | [[22](#_ENREF_22)] | | |
| Annual eye screening | 757.42 | [[22](#_ENREF_22)] | | |
|  |  |  | | |
| **Direct Costs CVD Complications** |  |  | | |
| Myocardial infarction 1st year | 146,950 | [[23](#_ENREF_23)] | | |
| Myocardial infarction 2nd+ years | 3,585 | [[23](#_ENREF_23)] | | |
| Angina 1st year | 146,950 | [[23](#_ENREF_23)] | | |
| Angina 2nd+ years | 3,585 | [[23](#_ENREF_23)] | | |
| Congestive heart failure 1st year | 127,449 | [[23](#_ENREF_23)] | | |
| Congestive heart failure 2nd plus years | 3,346 | [[23](#_ENREF_23)] | | |
| Stroke 1st year | 121,729 | [[24](#_ENREF_24)] | | |
| Stroke 2nd+ years | 21,628 | [[24](#_ENREF_24)] | | |
| Stroke death within 30 days | 59,731 | [[25](#_ENREF_25)] | | |
| Peripheral vascular disease 1st year | 23,103 | [[25](#_ENREF_25)] | | |
| Peripheral vascular disease 2nd+ years | 4,188 | [[26](#_ENREF_26)] | | |
|  |  |  | | |
| **Direct Costs Renal Complications** |  |  | | |
| Haemodialysis 1st year | 514,588 | [[27](#_ENREF_27)] |
| Haemodialysis 2+ years | 514,588 | [[27](#_ENREF_27)] |
| Peritoneal dialysis 1st year | 149,230 | [[27](#_ENREF_27)] |
| Peritoneal dialysis 2+ years | 149,230 | [[27](#_ENREF_27)] |
| Renal transplant costs 1st year | 307,901 | [[28](#_ENREF_28)] |
| Renal transplant 2+ years | 25,379 | [[28](#_ENREF_28)] |
|  |  |  | | |
| **Direct Costs Acute Events** |  |  | | |
| Non-severe hypoglycemic event | 25.50 | [[29](#_ENREF_29)] | | |
| Severe hypoglycemic event 1 (requiring non-medical assistance) | 25.50 | [[29](#_ENREF_29)] | | |
| Severe hypoglycemic event 2 (requiring medical assistance) | 12,160 | [[29](#_ENREF_29)] | | |
|  |  |  | | |
| **Direct Costs Eye Disease** |  |  | | |
| Laser treatment | 2,061 | [[25](#_ENREF_25)] | | |
| Cataract operation | 8,970 | [[25](#_ENREF_25)] | | |
| Following cataract operation | 244,66 | [[22](#_ENREF_22)] | | |
| Blindness - year of onset | 87,280 | [[30](#_ENREF_30)] | | |
| Blindness - following years | 87,280 | [[30](#_ENREF_30)] | | |
|  |  |  | | |
| **Direct Costs Neuropathy/Foot Ulcer/Amputation** |  |  | | |
| Neuropathy, 1st year | 28,256 | [[24](#_ENREF_24)] | | |
| Neuropathy, 2nd+ years | 143.44 | [[20](#_ENREF_20)] | | |
| Cost of active ulcer | 13,794 | [[29](#_ENREF_29)] | | |
| Cost of Amputation (lower extremity) | 89,715 | [[24](#_ENREF_24)] | | |
| Cost of Amputation follow up | 15,989 | [[31](#_ENREF_31)] | | |

CDM: Core diabetes model; DKK: Danish Krone; AIP: Apotekets Indkøbspris (Pharmacy Purchase Price); ACE: angiotensin-converting enzyme; ARB: angiotensin-receptor blockers; GRP: Gross renal proteinuria; CVD: cardiovascular disease

Table S10: Utilities used in CDM

| Variable | Input values | Reference |
| --- | --- | --- |
| U T2D no complications | 0.785 | [[32](#_ENREF_32)] |
| DisU MI event | -0.055 | [[32](#_ENREF_32)] |
| U post MI | 0.73 | Calculated |
| DisU angina event | -0.09 | [[32](#_ENREF_32)] |
| U angina | 0.695 | Calculated |
| DisU heart failure event | -0.108 | [[32](#_ENREF_32)] |
| U heart failure | 0.677 | Calculated |
| DisU stroke event | -0.164 | [[32](#_ENREF_32)] |
| U post Stroke | 0.621 | Calculated |
| DisU PVD | -0.061 | [[32](#_ENREF_32)] |
| U PVD | 0.724 | Calculated |
| QoL microalbuminuria | 0 | Assumed null |
| U microalbuminuria | 0.785 | Calculated |
| DisU macroalbuminuria | -0.048 | [[32](#_ENREF_32)] |
| U macroalbuminuria | 0.737 | Calculated |
| DisU HD | -0.164 | [[32](#_ENREF_32)] |
| U HD | 0.621 | Calculated |
| DisU PD | -0.204 | [[32](#_ENREF_32)] |
| U PD | 0.581 | Calculated |
| U RT | 0.762 | [[32](#_ENREF_32)] |
| DisU BDR | -0.04 | [[32](#_ENREF_32)] |
| U BDR | 0.745 | Calculated |
| U BDR wrongly treated | 0.745 | Calculated |
| DisU PDR | -0.07 | [[32](#_ENREF_32)] |
| U PDR laser treated | 0.715 | Calculated |
| U PDR no Laser | 0.715 | Calculated |
| DisU ME | -0.04 | [[32](#_ENREF_32)] |
| U ME | 0.745 | Calculated |
| DisU SVL | -0.074 | [[32](#_ENREF_32)] |
| U SVL | 0.711 | Calculated |
| DisU cataract | -0.016 | [[32](#_ENREF_32)] |
| U cataract | 0.769 | Calculated |
| DisU neuropathy | -0.084 | [[32](#_ENREF_32)] |
| U neuropathy | 0.701 | Calculated |
| QoL healed ulcer | 0 | Assumed null |
| U healed ulcer | 0.785 | Calculated |
| QoL active ulcer | -0.17 | [[32](#_ENREF_32)] |
| U active ulcer | 0.615 | Calculated |
| DisU amputation event | -0.28 | [[32](#_ENREF_32)] |
| U post amputation | 0.505 | Calculated |
| Diminishing NSHE disutility | Yes | [[33](#_ENREF_33)] |
| DisU for SHE1 (during daytime) | -0.0137 | [[34](#_ENREF_34)] |
| DisU for SHE1 (nocturnal) | -0.0137 | [[34](#_ENREF_34)] |
| DisU for SHE2 (during daytime) | -0.0578 | [[34](#_ENREF_34)] |
| DisU for SHE2 (nocturnal) | -0.0578 | [[34](#_ENREF_34)] |
| DisU for UTI/GI | -0.00476 | Calculated based on [[35](#_ENREF_35)] and [[36](#_ENREF_36)] |

CDM: Core diabetes model; U: health state utility; T2: Type 2 diabetes; DisU: disutility of an event; MI: Myocardial infarction; PVD: Peripheral vascular disease; QoL: Quality of life; HD: Haemodialysis; PD: Peritoneal dialysis; RT: Renal transplant; BDR: Background Retinopathy; PDR: Proliferative diabetic retinopathy; ME: Macular edema; SVL: Severe vision loss; NSHE: Non-Severe Hypoglycaemia; SHE1: Severe hypoglycaemia rate (not requiring medical assistance); SHE2: Severe hypoglycaemia rate (requiring medical assistance); UTI/GI: urinary tract infection/gastrointestinal infection

Table S11: Scenario analysis results

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | LY | | QALY | | Cost (DKK) | | ICER |
| **Oral sema + met** | **Empa**  **+ met** | **Oral sema + met** | **Empa**  **+ met** | **Oral sema + met** | **Empa**  **+ met** | **Oral sema + met vs empa + met** |
| Base case (time horizon 50 years) | 13.21 | 13.21 | 8.78 | 8.75 | 447,633 | 387,786 | 1,930,548 |
| Time horizon 5 years | 4.31 | 4.31 | 3.00 | 2.98 | 99,767 | 86,282 | 612,931 |
| HbA1c threshold of 8% | 13.21 | 13.21 | 8.82 | 8.79 | 432,106 | 371,308 | 1,961,225 |
| 3 lines of therapy (discontinuation of oral sema and empa and switch to higher dose long-acting insulin alone in 3rd line) | 13.24 | 13.21 | 8.74 | 8.69 | 373,513 | 355,797 | 328,076 |
| Trial product estimand - 50 years | 13.20 | 13.22 | 8.81 | 8.76 | 446,914 | 388,438 | 1,124,537 |
| Trial product estimand - 3 lines of therapy (discontinuation of oral sema and empa and switch to higher dose long-acting insulin alone in 3rd line) | 13.24 | 13.22 | 8.76 | 8.70 | 373,869 | 356,279 | 293,175 |

LY: life years; QALY: quality-adjusted life years; DKK: Danish Krone; ICER: incremental cost-effectiveness ratio; sema: semaglutide; met: metformin; empa: empagliflozin; HbA1c: glycated haemoglobin A1c

Table S12: Breakdown of costs (DKK, per average patient)

| Breakdown of costs | Accumulated over 50 years | | Accumulated over 5 years | |
| --- | --- | --- | --- | --- |
|  | Oral semaglutide  + met | Empagliflozin  + met | Oral semaglutide + met | Empagliflozin  + met |
| Total | 447,633 | 387,786 | 99,767 | 86,282 |
| Treatment | 238,073 | 176,301 | 57,204 | 43,442 |
| Management | 10,631 | 10,615 | 3,630 | 3,627 |
| Cardiovascular disease | 80,247 | 79,622 | 18,416 | 18,215 |
| Renal disease | 8,388 | 8,323 | 1,981 | 1,820 |
| Ulcer/amputation/neuropathy | 16,412 | 16,670 | 4,455 | 4,692 |
| Eye disease | 92,044 | 94,287 | 13,681 | 13,954 |
| NSHE | 1,476 | 1,582 | 322 | 428 |
| SHE (req. nonmed. assistance) | 7 | 7 | 2 | 2 |
| SHE (req. med. assistance) | 355 | 380 | 75 | 102 |

DKK: Danish Krone; met: metformin; NSHE: No severe hypoglycemic events, SHE: Severe hypoglycemic events

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