



Cost-Effectiveness Analysis of Fixed-Dose Triple Combination Therapy (Linagliptin/Metformin/Empagliflozin) vs. its Fixed Dose Double Combination and Individual Components in Type-2 Diabetes

Debra Winberg, MSc MA and Lizheng Shi, PhD, MsPharm, MA
Department of Health Policy and Management, School of Public Health and Tropical Medicine, Tulane University

INTRODUCTION

- In the past 30 years, the prevalence of type 2 diabetes (T2D) increased by 11%.^{1,2} In the United States, **almost 10% of people are living with T2D**.^{1,2}
- Uncontrolled T2D leads to complications** including heart disease, retinopathy, nephropathy, and neuropathy.³
- There are **10 classes** of drugs to treat T2D.⁴ Although metformin is the first-line treatment for T2D, many people do not reach glycemic control with metformin alone.⁵
- The American Diabetes Association recommends the **addition of a second-line drug** instead of switching drug classes – oral combination therapy.⁶
- Patients on oral combination therapy take **one pill with multiple compounds**, a fixed-dose combination (FDC) or multiple pills of one compound, a loose-dose combination (LDC).⁴
- There are several benefits for choosing an FDC over an LDC **including increasing adherence, reducing costs, and increasing glycemic control**.^{7,8,9}
- Trijardy XR was released on the U.S. market in January 2021. It is a single pill containing metformin XR, a DPP-4 inhibitor and a sodium-glucose co-transporter 2 inhibitor (SGLT2).

AIM

To compare the **lifetime cost-effectiveness** of once-daily 25 mg **Empagliflozin/5 mg Linagliptin/1000 mg Metformin XR triple-fixed-dose** combination (**Triple FDC**) versus:

- 5 mg Linagliptin/25 mg Empagliflozin FDC + 1000 mg metformin XR (**Double FDC**)
- 5 mg Linagliptin + 1000 mg metformin XR (**Linagliptin**)
- 25 mg Empagliflozin + 1000 mg metformin XR (**Empagliflozin**)

METHODS

The Building, Relating, Assessing, and Validating Outcomes (BRAVO) diabetes model was used to assess costs and outcomes with an antidiabetic FDC vs. its equivalent formulations from a US national health payer perspective. This is validated, person-level discrete-time microsimulation which simulates the progression of diabetes complications based on individuals' dynamic characteristics and treatment regimens.

Perspective	Health-system
Time Horizon	40-years
Discount Rate	3.0% for costs and QALYs
Primary Clinical Trials	<ul style="list-style-type: none"> NCT01422876 (Defronzo)¹⁰ Manufacture study (Boehringer-Ingelheim)¹¹ ACCORD Trial¹²
Study population	Simulation with 1000 runs of a cohort of 1000 patients living with T2D whose T2D is not controlled by metformin

MODEL INPUTS

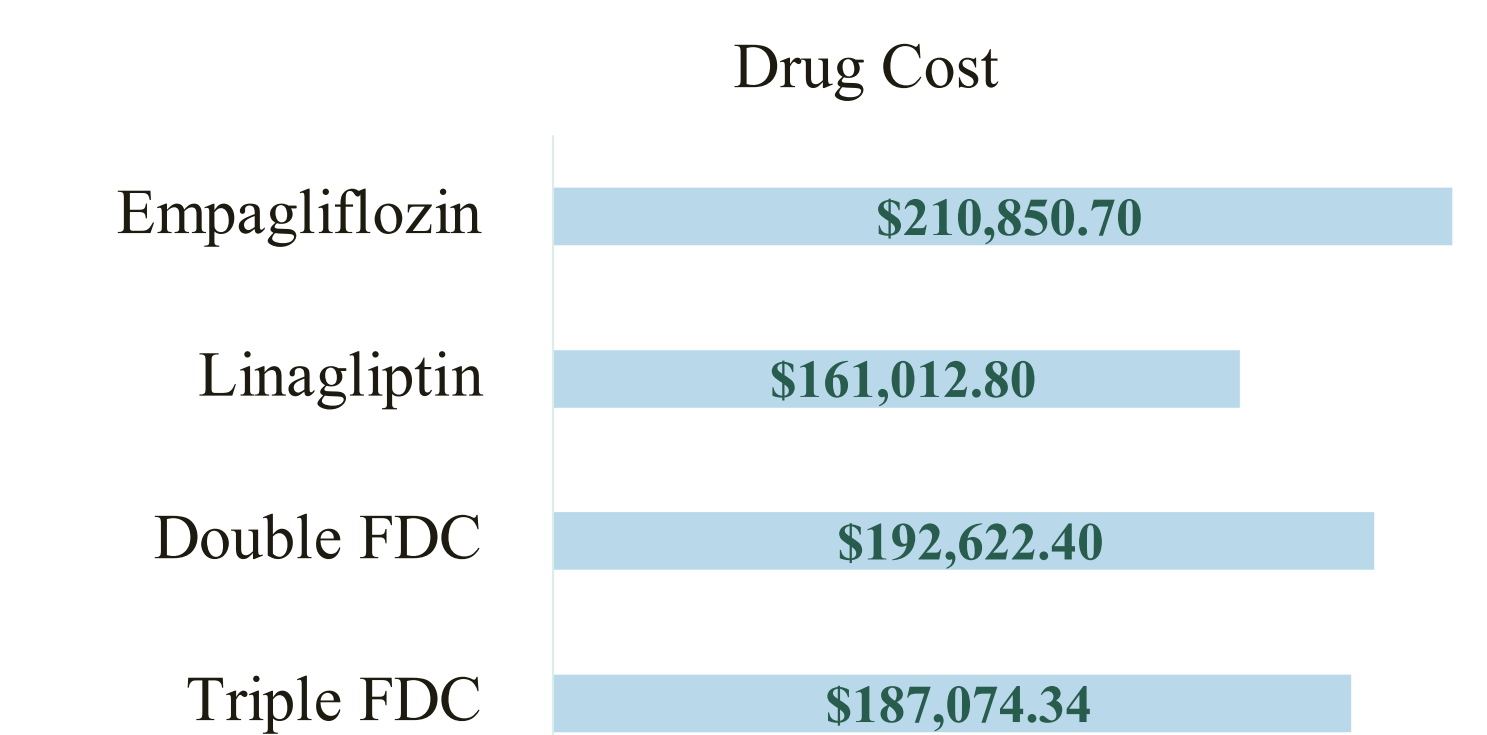
	Cost per Month	Annual Cost	Citation
Empagliflozin/linagliptin/metformin	\$683.27	\$8,199.24	Good RX
Empagliflozin/linagliptin+metformin	\$703.38	\$8,440.56	Good RX
Linagliptin + metformin	\$598.25	\$7,179.00	Good RX
Empagliflozin + metformin	\$773.89	\$9,286.68	Good RX

	Cost per Month	Annual Cost	Citation	Diabetes Risk Factors			
Empagliflozin/linagliptin/metformin	\$683.27	\$8,199.24	Good RX	HbA1c (%)	Mean	SE	Citation
Empagliflozin/linagliptin+metformin	\$703.38	\$8,440.56	Good RX	LDL	46.85	1.8	DeFronzo
Linagliptin + metformin	\$598.25	\$7,179.00	Good RX	SBP	130.9	15.7	DeFronzo
Empagliflozin + metformin	\$773.89	\$9,286.68	Good RX	Weight (kg)	85.5	20.4	DeFronzo

Treatment		Mean	SE	Citation
Empagliflozin/linagliptin/metformin	HbA1c	-1.3	0.06	Boehringer Ingelheim
	LDL	0.1	0.1	DeFronzo
	HDL	0.1	0	DeFronzo
	SBP	-3.6	0.91	DeFronzo
Empagliflozin/linagliptin+metformin	Weight	-2.9	0.1	Boehringer Ingelheim
	HbA1c	-1.2	0.06	DeFronzo
	LDL	0.1	0.1	DeFronzo
	HDL	0.1	0	DeFronzo
Linagliptin + metformin	SBP	-3.6	0.91	DeFronzo
	Weight	-3	0.1	DeFronzo
	HbA1c	-0.71	0.07	DeFronzo
	LDL	0	0.1	DeFronzo
Empagliflozin + metformin	HDL	0	0	DeFronzo
	SBP	0.3	0.38	DeFronzo
	Weight	-0.7	0.1	DeFronzo
	HbA1c	-0.64	0.06	DeFronzo

Clinical trial data for 24 weeks

RESULTS

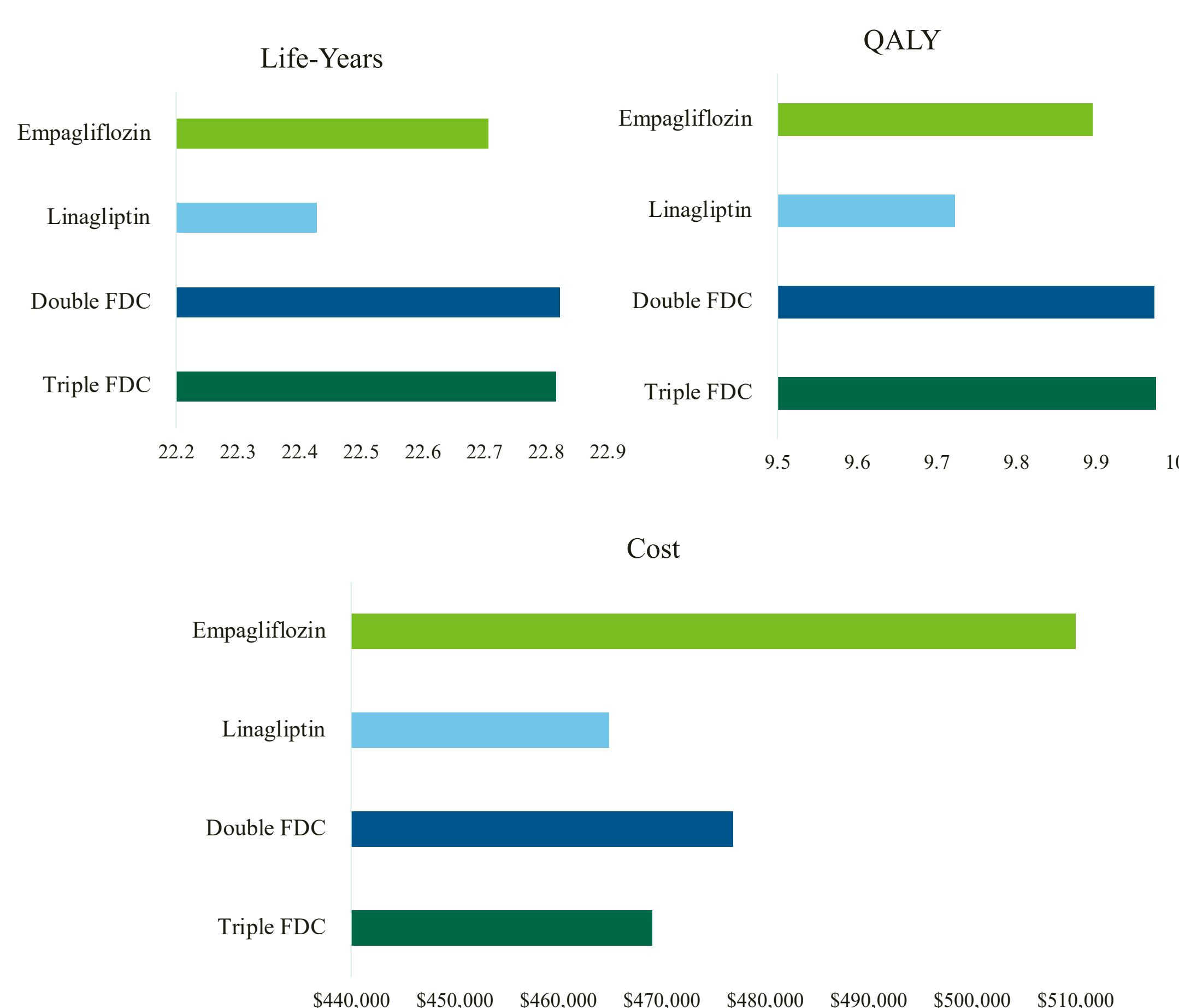


Drug costs include Metformin plus the single or double pill for the comparison groups. Costs are similar between the Triple FDC and Double FDC group, higher in the Empagliflozin group, and lower in the Linagliptin group.

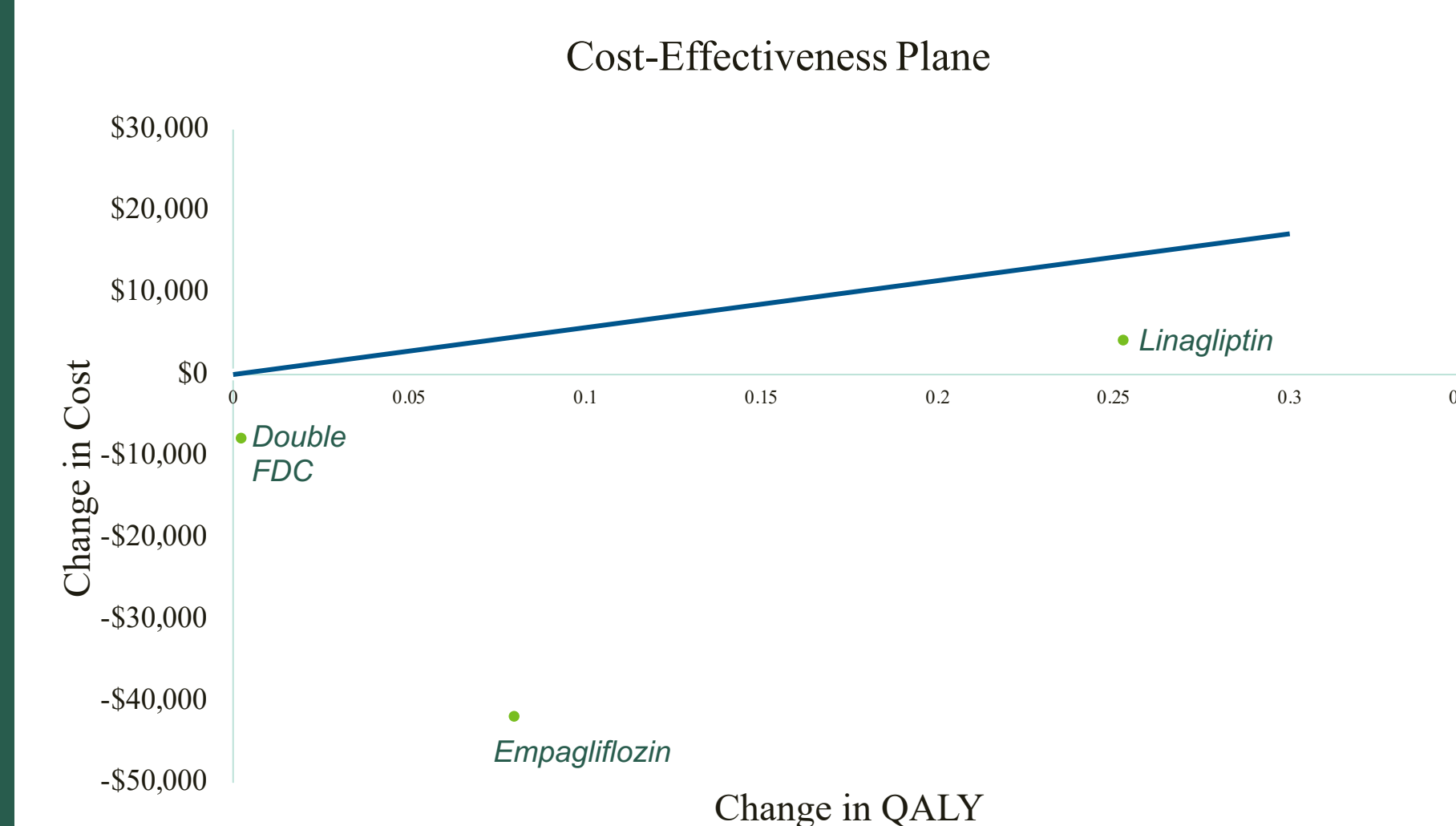
Difference in Complications Between Treatment and Comparisons

Complication	Double FDC	Linagliptin	Empagliflozin
Stroke	0.30%	2.52%	2.15%
Non-Fatal Stroke	0.21%	1.83%	1.56%
Fatal Stroke	0.10%	0.69%	0.60%
MI	0.30%	1.33%	2.07%
Non-Fatal MI	0.28%	1.20%	1.87%
Fatal MI	0.03%	0.13%	0.20%
CHF	0.26%	3.67%	1.73%
Non-Fatal CHF	0.09%	1.13%	0.54%
Fatal CHF	0.17%	2.53%	1.19%
Angina	0.16%	1.21%	1.19%
Revascularization	0.19%	2.73%	1.40%
ESRD	0.12%	1.48%	1.18%
Blind	0.39%	2.82%	2.68%
SPSL	0.88%	5.25%	5.54%
All Cause Mortality	0.00%	0.70%	0.28%
CVD Mortality	0.00%	0.00%	0.00%
MACE Component	0.45%	2.88%	3.25%

RESULTS



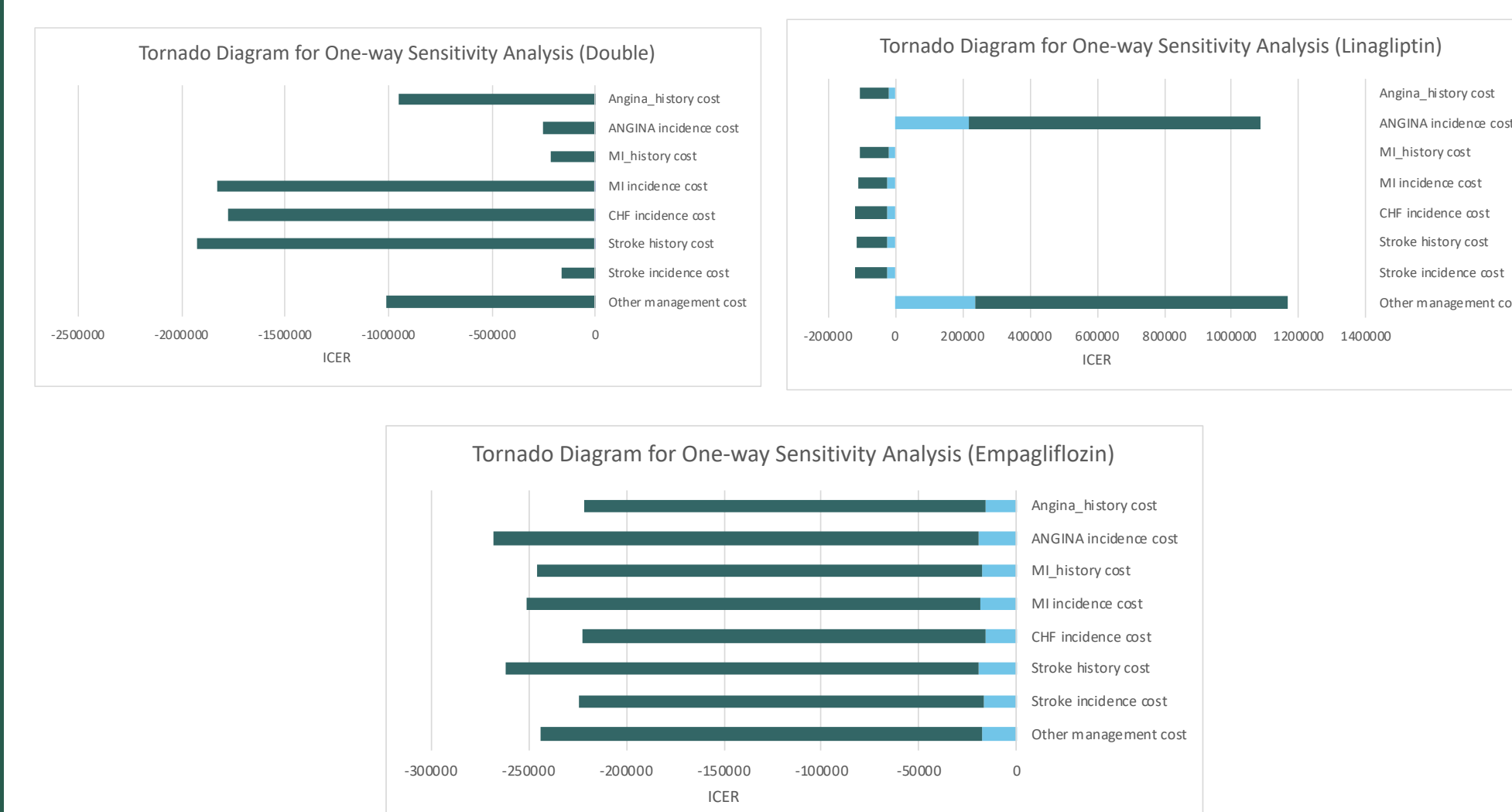
RESULTS



Comparator	Cost Compared to Triple	Effectiveness Compared to Triple	Conclusion
Double FDC	Less Costly	More Effective	Triple is dominant
Linagliptin	More Costly	More Effective	Triple is cost-effective
Empagliflozin	Less Costly	More Effective	Triple is dominant

Sensitivity Analyses

Probabilistic sensitivity analysis found that results were cost-effective 100% of the time at the \$50,000/QALY threshold.



Limitations

- Assumptions:** Several assumptions were made. 1) All group histories were the same as the Double FDC group and the ACCORD data could be used for missing data. 2) If no clinical outcome data was given for the Triple FDC group, the outcomes were assumed to be equal to the Double FDC group.
- Triple FDC Data:** Unclear information on triple FDC group (data from Boehringer Ingelheim website)
- Adherence:** Data from clinical trials but adherence is a large driver of improved outcomes in FDCs

DISCUSSION and CONCLUSION

- In the base case analysis, the triple FDC treatment demonstrated to be a dominant alternative to double FDC + Metformin and Empagliflozin + Metformin and cost-effective compared to Linagliptin + Metformin
- The results hold in sensitivity analyses and are most sensitive to angina and other medication costs
- Patients with uncontrolled diabetes with metformin should be prescribed Trijardy XR

Citations

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