

# **Cost-Utility and Budget Impact Analysis of Adding SGLT-2 inhibitor to Standard Treatment in Type 2 Diabetes Patients with Heart Failure, Utilizing National Database Insights from Thailand.**

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## **• Competing interests**

The authors have thoroughly reviewed and disclosed all relevant information. We confirm that there are no financial or non-financial interests—such as professional interests, personal relationships, or personal beliefs—that could be perceived as influencing the work reported in this manuscript. This disclosure is made in strict accordance with the journal's guidelines to ensure full transparency and prevent any potential bias in the research presented.

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## Supplementary materials

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## Appendix A. Search term for each database

- **MEDLINE via PubMed**

((("heart failure"[MeSH Terms] OR "heart failure" OR "cardiac failure" OR HF OR CHF) OR (diabetes OR diabetic OR "diabetes mellitus" OR "type 2 diabetes mellitus" OR T2DM OR "Diabetes Mellitus"[Mesh])) AND ("Sodium-Glucose Transporter 2 Inhibitors"[Mesh] OR "SGLT2 inhibitors"[All Fields] OR "sodium-glucose cotransporter-2 inhibitors"[All Fields] OR "sodium-glucose transporter 2"[MeSH] OR "empagliflozin"[All Fields] OR "Tofogliflozin"[All Fields] OR "canagliflozin"[All Fields] OR "Luseogliflozin"[All Fields] OR "Dapagliflozin"[All Fields] OR "Ertugliflozin"[All Fields] OR "Ipragliflozin"[All Fields] OR "bexagliflozin"[All Fields] OR "henagliflozin"[All Fields] OR "Licogliflozin"[All Fields] OR "remogliflozin"[All Fields] OR "sergliflozin"[All Fields] OR "sotagliflozin"[All Fields])) AND ("Heart failure hospitalization" OR "death" OR mortality [MeSH] OR "all-cause mortality" OR "cardiovascular mortality")

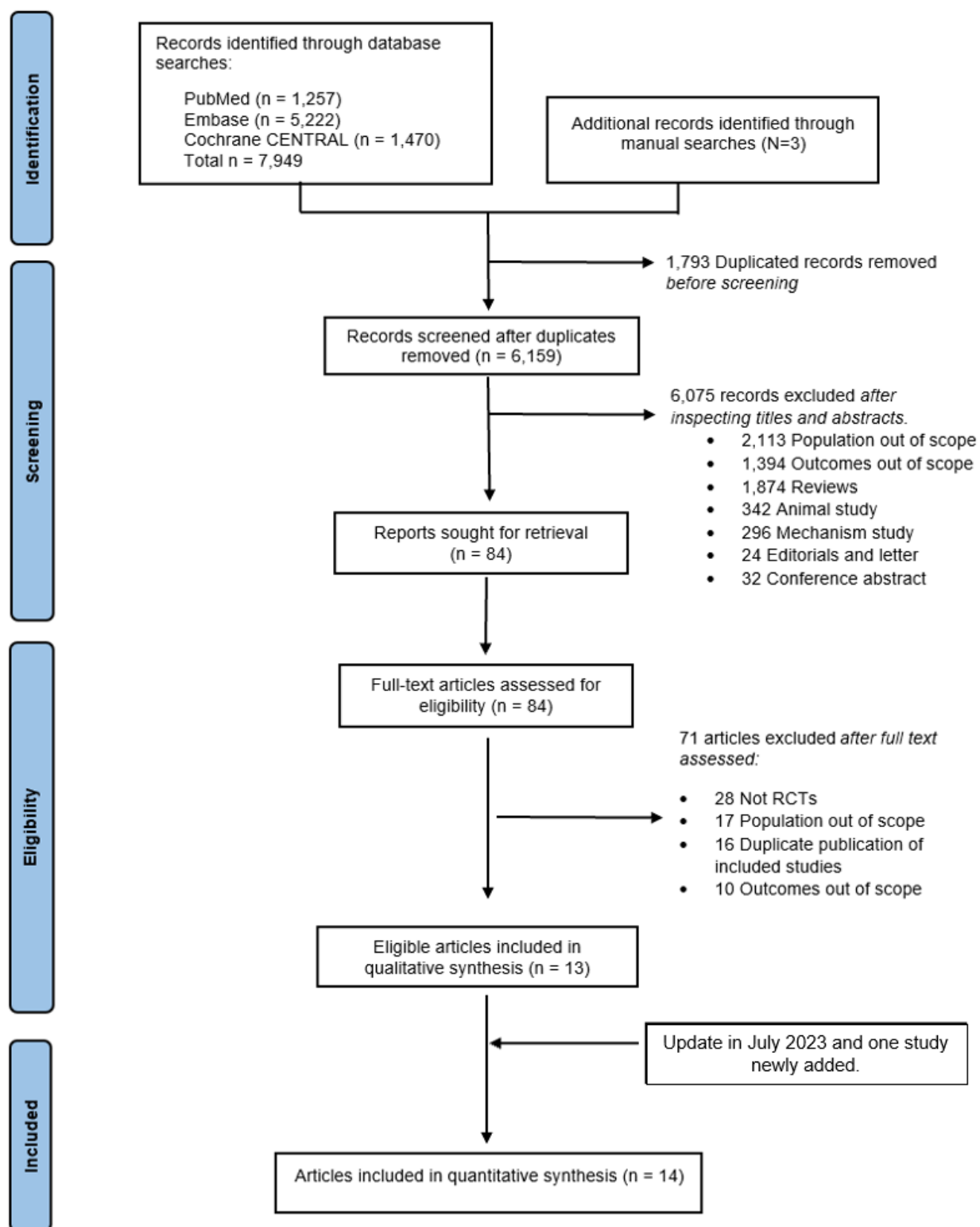
- **EMBASE (Elsevier)**

((('heart failure'/exp OR 'heart failure' OR 'cardiac failure' OR HF OR CHF ) OR (diabetes OR diabetic OR 'diabetes mellitus' OR 'type 2 diabetes mellitus' OR T2DM OR 'Diabetes Mellitus'/exp)) AND ('sodium glucose cotransporter 2 inhibitor'/exp OR 'SGLT2 inhibitors' OR 'sodium-glucose cotransporter-2 inhibitors' OR 'sodium glucose cotransporter 2'/exp OR empagliflozin OR Tofogliflozin OR canagliflozin OR Luseogliflozin OR Dapagliflozin OR Ertugliflozin OR Ipragliflozin OR bexagliflozin OR henagliflozin OR Licogliflozin OR remogliflozin OR sergliflozin OR sotagliflozin)) AND ('Heart failure hospitalization' OR death OR mortality/exp OR 'all-cause mortality' OR 'cardiovascular mortality')

- **Central (OVID)**

((exp Heart Failure/ OR "heart failure" OR "cardiac failure" OR HF OR CHF) OR (diabetes OR diabetic OR "diabetes mellitus" OR "type 2 diabetes mellitus" OR T2DM OR exp Diabetes Mellitus/)) AND (exp Sodium-Glucose Transporter 2 Inhibitors/ OR "SGLT2 inhibitors".af. OR "sodium-glucose cotransporter-2 inhibitors".af. OR empagliflozin.af. OR Tofogliflozin.af. OR canagliflozin.af. OR Luseogliflozin.af. OR Dapagliflozin.af. OR Ertugliflozin.af. OR Ipragliflozin.af. OR bexagliflozin.af. OR henagliflozin.af. OR Licogliflozin.af. OR remogliflozin.af. OR sergliflozin.af. OR sotagliflozin.af.)) AND ("Heart failure hospitalization" OR death OR exp Mortality/ OR "all-cause mortality" OR "cardiovascular mortality")

## Appendix B. PRISMA flow diagram

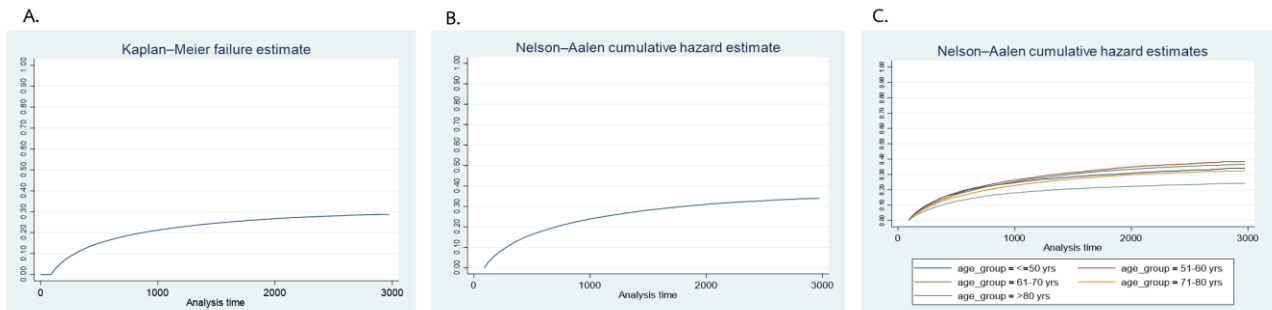


**Appendix C.** Characteristics of the included studies used in the systematic review and network meta-analysis.

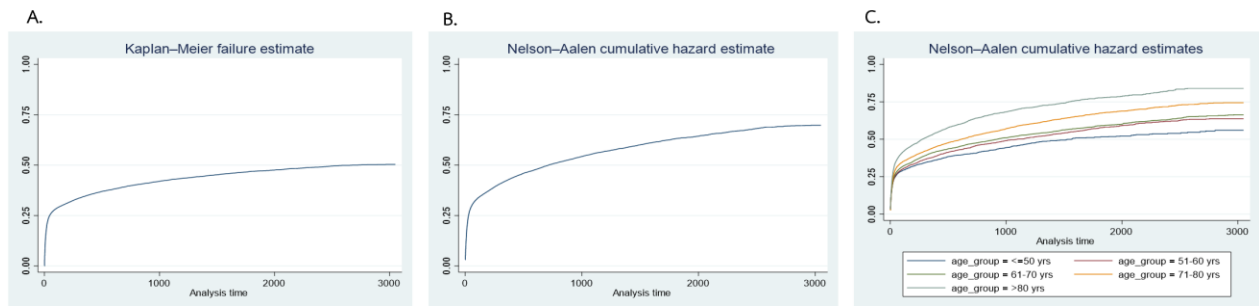
| Study, year             | N    | Intervention  | Dose (mg/d) | Follow up (years) | Age (years) | Female, % | Duration of DM (years) | HbA1C (%) | BMI (kg/m <sup>2</sup> ) | LVEF, % | NT-proBNP (pg/ml) | eGFR (ml/min/1.73m <sup>2</sup> ) | NYHA II | NYHA III | NYHA IV |
|-------------------------|------|---------------|-------------|-------------------|-------------|-----------|------------------------|-----------|--------------------------|---------|-------------------|-----------------------------------|---------|----------|---------|
| EMPA-REG, 2016          | 706  | Empagliflozin | 10, 25      | 3.1               | 64.50       | 29.90     | NA                     | 8.08      | 32.04                    | NA      | NA                | 68.71                             | NA      | NA       | NA      |
| CANVAS Program, 2018    | 1461 | Canagliflozin | 100, 300    | 3.6               | 63.78       | 44.36     | 12.04                  | 8.40      | 33.15                    | NA      | NA                | 72.97                             | NA      | NA       | NA      |
| DECLARE-TIMI 58, 2019   | 1987 | Dapagliflozin | 10          | 4.2               | 64.16       | 33.68     | 10.08                  | 8.27      | 32.83                    | 48.9    | NA                | 83.57                             | 56.07   | 7.75     | NA      |
| DAPA-HF, 2020           | 2139 | Dapagliflozin | 10          | 1.5               | 66.50       | 22.30     | 7.76                   | 7.40      | 29.35                    | 31.2    | 1483.0            | 63.35                             | 63.64   | 35.26    | 1.00    |
| VERTIS-CV, 2020         | 1958 | Ertugliflozin | 5, 15       | 3.5               | 64.37       | 31.87     | 12.04                  | 8.30      | 32.57                    | NA      | NA                | NA                                | 65.85   | 7.08     | 0.07    |
| SCORED, 2021            | 3283 | Sotagliflozin | 200, 400    | 1.3               | NA          | NA        | NA                     | NA        | NA                       | NA      | NA                | NA                                | NA      | NA       | NA      |
| SOLOIST-WHF, 2021       | 1222 | Sotagliflozin | 200         | 0.8               | 69.63       | 33.76     | 10.59                  | 7.24      | 30.68                    | 36.0    | 2006.5            | 50.37                             | 45.17   | 45.83    | 4.42    |
| EMPEROR-reduced, 2021   | 1856 | Empagliflozin | 10          | 1.3               | 66.70       | 23.10     | NA                     | 7.40      | 28.70                    | 27.4    | 1915.5            | 61.20                             | 71.40   | 27.90    | 0.70    |
| CANONICAL, 2021         | 82   | Canagliflozin | 100         | 0.5               | 75.70       | 32.90     | 7.08                   | 7.01      | 25.00                    | 61.5    | 141.0             | 57.00                             | 91.50   | 8.50     | NA      |
| EMPEROR-preserved, 2022 | 2938 | Empagliflozin | 10          | 2.2               | 70.90       | 42.80     | NA                     | 7.26      | 31.05                    | 53.9    | 907.0             | 59.70                             | 79.40   | 20.40    | 0.20    |
| DELIVER, 2022           | 2806 | Dapagliflozin | 10          | 2.3               | 71.65       | 43.90     | NA                     | NA        | 29.85                    | 54.1    | 796.1             | 61.00                             | 75.25   | 24.45    | 0.30    |

## Appendix D. Survival analysis of each transitional probability

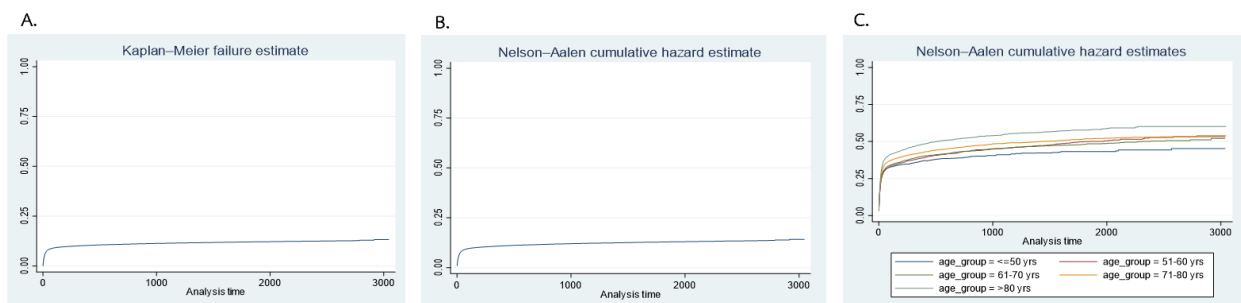
- Survival analysis of stable heart failure to heart failure hospitalization. A) Kaplan-Meier failure, B) cumulative hazard ratio, C) cumulative hazard ratio stratified by age group. (Analysis time in days)



- Survival analysis of stable heart failure to death. A) Kaplan-Meier failure, B) cumulative hazard ratio, C) cumulative hazard ratio stratified by age group. (Analysis time in day)



- Survival analysis of heart failure hospitalization to death. A) Kaplan-Meier failure, B) cumulative hazard ratio, C) cumulative hazard ratio stratified by age group. (Analysis time in day)



**Appendix E.** Baseline characteristics of the cohort population.

| <b>Characteristics</b>                                                                                                                                                                                     | <b>Values</b>                                                                                       |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------|
| Overall age (years) <ul style="list-style-type: none"> <li>• Mean <math>\pm</math> SD</li> <li>• Median (IQR)</li> </ul>                                                                                   | 67.7 $\pm$ 12.27<br>68 (60-77)                                                                      |
| Female age (years) <ul style="list-style-type: none"> <li>• Mean <math>\pm</math> SD</li> <li>• Median (IQR)</li> </ul>                                                                                    | 69.1 $\pm$ 12.1<br>70 (62-78)                                                                       |
| Male age (years) <ul style="list-style-type: none"> <li>• Mean <math>\pm</math> SD</li> <li>• Median (IQR)</li> </ul>                                                                                      | 65.5 $\pm$ 12.3<br>66 (58-74)                                                                       |
| Age group, N (%) <ul style="list-style-type: none"> <li>• <math>\geq 50</math> years</li> <li>• 51-60 years</li> <li>• 61-70 years</li> <li>• 71-80 years</li> <li>• <math>&gt; 80</math> years</li> </ul> | 3,748 (8.4%)<br>7,897 (17.7%)<br>13,697 (30.7%)<br>12,581 (28.2%)<br>6,737 (15.1%)                  |
| Sex, N (%) <ul style="list-style-type: none"> <li>• Female</li> <li>• Male</li> </ul>                                                                                                                      | 27,171 (60.9%)<br>17,444 (39.1%)                                                                    |
| Comorbidities, N (%) <ul style="list-style-type: none"> <li>• CCI = 1</li> <li>• CCI = 2</li> <li>• CCI = 3</li> <li>• CCI = 4</li> <li>• CCI <math>\geq 5</math></li> </ul>                               | 12,715 (28.5%)<br>18,872 (42.3%)<br>9,057 (20.3%)<br>2,989 (6.7%)<br>1,026 (2.3%)                   |
| Age-adjusted CCI, N (%) <ul style="list-style-type: none"> <li>• ACCI = 2-3</li> <li>• ACCI = 4</li> <li>• ACCI = 5</li> <li>• ACCI = 6</li> <li>• ACCI = 7</li> <li>• ACCI <math>\geq 8</math></li> </ul> | 5,086 (11.4%)<br>7,674 (17.2%)<br>10,841 (24.3%)<br>10,886 (24.4%)<br>6,871 (15.4%)<br>3,257 (7.3%) |
| Overall median survival <ul style="list-style-type: none"> <li>• 71-80 years</li> <li>• <math>&gt; 80</math> years</li> </ul>                                                                              | 7.32 years<br>5.62 years<br>2.87 years                                                              |
| Risk of rehospitalization                                                                                                                                                                                  | 36,538/133,616 (27.4%)                                                                              |

CCI: Charlson comorbidity index, ACCI: age-adjusted Charlson comorbidity index.

## Appendix F. Extended cost-effectiveness of SGLT-2 inhibitors

League tables that rank alternative healthcare interventions based on their quality-adjusted life year (QALYs)<sup>(1)</sup> was applied. The ICER for a given treatment alternative is higher than that of the next, more effective, alternative <sup>(2)</sup>. In this case, the extended incremental cost-effectiveness ratio (ICER) is calculated by comparing the differences in costs and QALYs between each SGLT-2 inhibitor and the standard treatment. This ratio reflects the cost per additional QALY gained.

| <b>Treatment option</b> | <b>Total lifetime cost<br/>(societal perspective)</b> | <b>QALY</b> | <b>Extended ICER</b> |
|-------------------------|-------------------------------------------------------|-------------|----------------------|
| Standard treatment      | 6,082                                                 | 3.73        |                      |
| Empagliflozin           | 8,776                                                 | 3.79        | 44,900               |
| Dapagliflozin           | 9,628                                                 | 4.27        | 1,775                |
| Canagliflozin           | 11,682                                                | 4.95        | 3,020                |

### Reference:

1. Mauskopf J, Rutten F, Schonfeld W. Cost-effectiveness league tables: valuable guidance for decision makers? *Pharmacoeconomics*. 2003;21(14):991-1000.
2. Drummond MF, Sculpher MJ, Torrance GW, O'Brien BJ, Stoddart GL. *Methods for the economic evaluation of health care program* 3<sup>rd</sup> edition. Oxford University Press Inc., New York. 2005

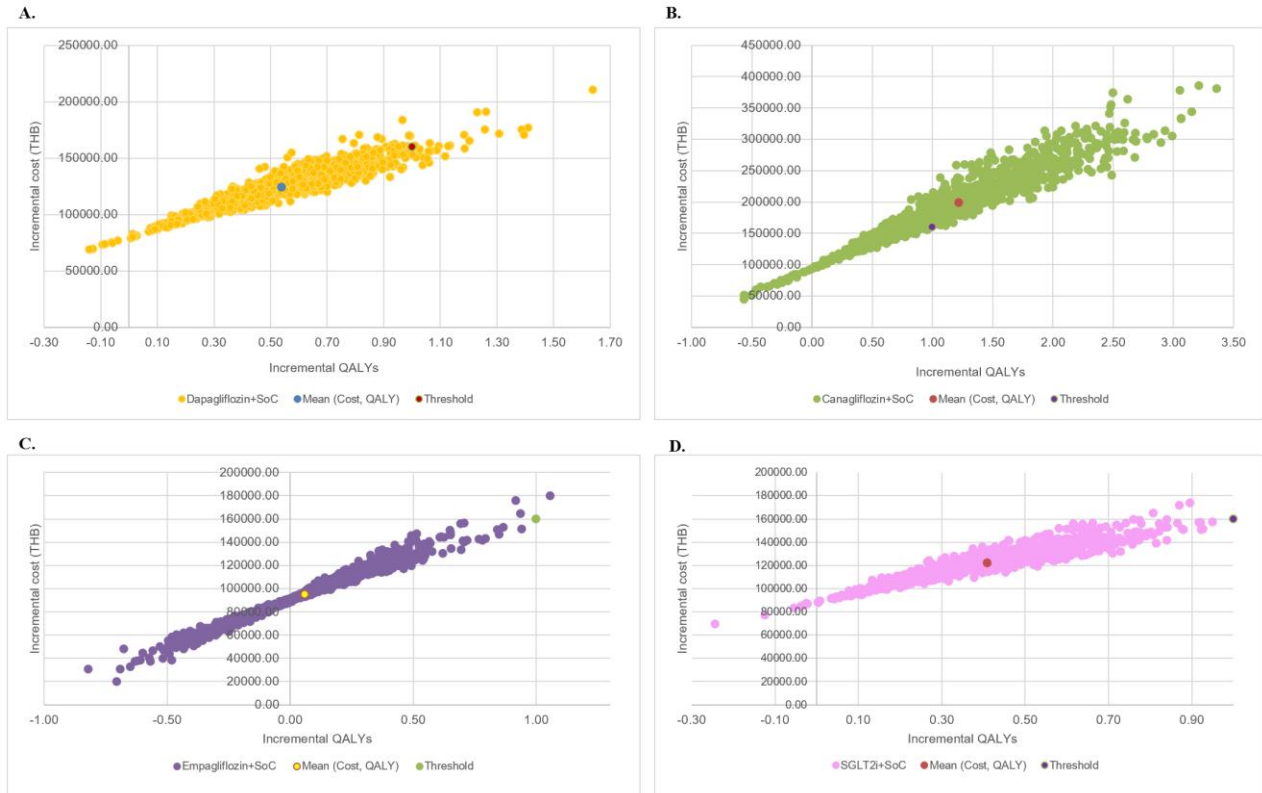
**Appendix G.** Cost-utility analysis results from the scenario analysis using utility data from other countries (societal perspective)

|                                    | Treatment options |                        |                        |                        |                           |
|------------------------------------|-------------------|------------------------|------------------------|------------------------|---------------------------|
|                                    | SoC               | Dapagliflozin<br>+ SoC | Canagliflozin<br>+ SoC | Empagliflozin<br>+ SoC | SGLT-2 inhibitor<br>+ SoC |
| Total cost† (no discount)          | 6,435             | 10,200                 | 12,536                 | 9,287                  | 10,132                    |
| Total cost† (discount)*            | 6,097             | 9,631                  | 11,772                 | 8,804                  | 9,577                     |
| Life years (no discount)           | 6.47              | 7.38                   | 8.53                   | 6.55                   | 7.15                      |
| Life years (discount)*             | 5.92              | 6.76                   | 7.82                   | 6.00                   | 6.55                      |
| QALY (no discount)                 | 3.94              | 4.54                   | 5.25                   | 4.00                   | 4.38                      |
| QALY (discount)*                   | 3.75              | 4.30                   | 4.96                   | 3.81                   | 4.16                      |
| Incremental cost† (discount)*      | Reference         | 3,534                  | 5,675                  | 2,707                  | 3,480                     |
| Incremental life years (discount)* | Reference         | 0.84                   | 1.90                   | 0.08                   | 0.63                      |
| Incremental QALY (discount)*       | Reference         | 0.69                   | 1.51                   | 0.07                   | 0.51                      |
| ICER per QALY† (discount)*         | Reference         | 5,122                  | 3,758                  | 38,671                 | 6,824                     |

†Cost presented in U.S. dollars with a conversion rate of 35.06 THB per U.S. dollar.

\*Discount of 3% per year, QALY: quality adjusted life year, ICER: incremental cost-effectiveness ratio

**Appendix H.** Scatter plots showing the incremental costs and incremental quality-adjusted life-year values from one thousand simulations. A) Dapagliflozin, B) Canagliflozin, C) Empagliflozin, D) SGLT-2 inhibitor



**Appendix I. Model validation:** Kaplan-Meier curves of all-causes of death from the heart failure cohort study in Thailand compared to the cumulative all-causes of death from the analytical model.

