SUPPLEMENTAL MATERIAL

Table S1. Electronic Search Terms.

| 1 | canagliflozin.mp. or Canagliflozin/ |
|-----|--|
| 2 | dapagliflozin.mp. |
| 3 | empagliflozin.mp. |
| 4 | ertugliflozin.mp. |
| 5 | type 2 diabetes mellitus.mp. or Diabetes Mellitus, Type 2/ |
| 6 | Diabetes Mellitus, Type 2/ or T2DM.mp. |
| 7 | Coronary Disease/ or Cardiovascular Diseases/ or Myocardial Infarction/ or cardiovascular mortality.mp |
| 8 | Acute Coronary Syndrome/ |
| 9 | heart failure.mp. or Heart Failure/ |
| 10 | Stroke/ |
| 11 | Mortality/ |
| 12 | 1 or 2 or 3 or 4 |
| 13 | 5 or 6 |
| 14 | 7 or 8 or 9 or 10 or 11 |
| 15 | 12 and 13 and 14 |
| 16. | Limit 15 human |
| EN | IBASE via OVID |
| 1 | canagliflozin.mp. or Canagliflozin/ |
| 2 | dapagliflozin.mp. |
| 3 | empagliflozin.mp. |
| 4 | ertugliflozin.mp. |
| 5 | type 2 diabetes mellitus.mp. or Diabetes Mellitus, Type 2/ |
| 6 | Diabetes Mellitus, Type 2/ or T2DM.mp. |
| 7 | Coronary Disease/ or Cardiovascular Diseases/ or Myocardial Infarction/ or cardiovascular mortality.mp |
| 8 | Acute Coronary Syndrome/ |
| 9 | heart failure.mp. or Heart Failure/ |
| 10 | Stroke/ |
| 11 | Mortality/ |
| 12 | 1 or 2 or 3 or 4 |
| 13 | 5 or 6 |
| 14 | |
| 15 | 12 and 13 and 14 |
| 16. | Limit 15 human |
| 10. | |

Table S2. Risk of Bias Assessment.

| | Sequence generation | Allocation sequence concealment | Blinding of participants and | Blinding of outcome assessment | Incomplete outcome data | Selective outcome reporting |
|-----------------|------------------------|------------------------------------|---------------------------------|-----------------------------------|----------------------------|--------------------------------|
| | | | personnel | | | |
| EMPA-REG | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk |
| CANVAS Program | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk |
| DECLARE-TIMI 58 | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk |
| CREDENCE | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk |



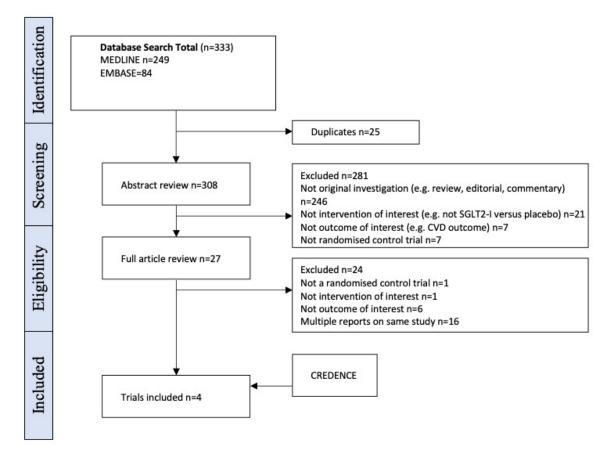


Figure S2A. Effects of SGLT2 inhibition on MACE, CV death, total MI and total stroke for patients with (secondary prevention) and without (primary prevention) cardiovascular disease at baseline.

| : Event | | | |
|--------------------|---|--|--|
| Litter | | | |
| 4687 | 2333 | | 0.86 (0.74, 0.99 |
| 5795 | 4347 | | 0.86 (0.75, 0.97 |
| 8582 | 8578 | | 0.93 (0.84, 1.03 |
| 2202 | 2199 | | 0.80 (0.67, 0.95 |
| = 0.0%, p = | = 0.477) | \diamond | 0.88 (0.82, 0.94 |
| n 4687 | 2333 | | 0.86 (0.74, 0.99 |
| | | | 0.82 (0.72, 0.95 |
| 3474 | | | 0.90 (0.79, 1.02 |
| 1113 | 1107 | _ _ | 0.85 (0.69, 1.06 |
| = 0.0%, p = | 0.813) | \diamond | 0.86 (0.80, 0.93 |
| 2039 | 1447 | | 0.98 (0.74, 1.30 |
| 5108 | 5078 | | 1.01 (0.86, 1.20 |
| 1089 | 1092 | — — —————————————————————————————————— | 0.68 (0.49, 0.93 |
| = 57.6%, p | = 0.094) | \diamond | 0.94 (0.82, 1.07 |
| | | | |
| 4687 | 2333 | _ | 0.62 (0.49, 0.77 |
| | | _ | 0.87 (0.72, 1.06 |
| | | | 0.98 (0.82, 1.17 |
| | | | 0.78 (0.61, 1.00 |
| | | \diamond | 0.83 (0.75, 0.92 |
| n | | | |
| 4687 | 2333 | _ _ | 0.62 (0.49, 0.77 |
| 3756 | 2900 | _ _ | 0.86 (0.70, 1.06 |
| 3474 | 3500 | | 0.94 (0.76, 1.18 |
| 1113 | 1107 | | 0.79 (0.58, 1.07 |
| | | $\overline{\diamond}$ | 0.80 (0.71, 0.90 |
| | | | |
| 2039 | 1447 | | 0.93 (0.60, 1.43 |
| 5108 | 5078 | | 1.06 (0.79, 1.42 |
| 1089 | 1092 | | 0.75 (0.48, 1.16 |
| = 0.0%, p = | = 0.439) | | 0.95 (0.77, 1.17 |
| fatal and no | on-fatal) | | |
| 4687 | 2333 | | 0.87 (0.70, 1.09 |
| | | | 0.89 (0.73, 1.09 |
| | | | 0.89 (0.77, 1.01 |
| | | | 0.86 (0.64, 1.16 |
| | | $\overline{\diamond}$ | 0.88 (0.80, 0.97 |
| 'n | | | |
| 4687 | 2333 | | 0.87 (0.70, 1.09 |
| 3756 | 2900 | | 0.82 (0.66, 1.01 |
| 3474 | 3500 | | 0.87 (0.74, 1.02 |
| 1113 | 1107 | | 0.93 (0.66, 1.32 |
| = 0.0%, p = | = 0.937) | \diamond | 0.86 (0.78, 0.96 |
| | | _ | |
| 2039 | 1447 | | 1.38 (0.84, 2.26 |
| | | | 0.94 (0.73, 1.21 |
| 1089 - 40.1% p | | | 0.69 (0.38, 1.21 |
| - 40.1%, p | - 0.169) | | 0.97 (0.78, 1.19 |
| atal) | | | |
| 4687 | 2333 | | 1.18 (0.89, 1.56 |
| 5795 | 4347 | _ _ | 0.87 (0.69, 1.09 |
| 8582 | 8578 | | 1.01 (0.84, 1.21 |
| 2202 | 2199 | _ _ | 0.77 (0.55, 1.07 |
| | = 0.189) | \diamond | 0.96 (0.86, 1.09 |
| n | | | |
| 4687 | 2333 | | 1.18 (0.89, 1.56 |
| 3756 | 2900 | | 0.82 (0.63, 1.06 |
| 3474 | 3500 | | 0.97 (0.76, 1.22 |
| 1113 = 19.3%, р | 1107 = 0.294) | | 0.87 (0.58, 1.31 0.96 (0.83, 1.10 |
| | | 1 | 2100 (2100) 1.11 |
| 2039 | 1447 | | 1 07 /0 66 4 7 |
| | | | 1.07 (0.66, 1.71 |
| | | | 1.09 (0.82, 1.45 |
| | | | 0.60 (0.33, 1.07 |
| - 39.0%, p | - 0.190) | | 0.99 (0.79, 1.25 |
| | | | |
| | 4687 5795 8582 2202 = 0.0%, p = 0.0%, p = 2039 5108 = 57.6%, p 4687 5795 8582 2202 = 70.7%, p 4687 3756 3474 1113 = 59.6%, p 2039 5108 1089 = 0.0%, p = fatal and nc 4687 5795 8582 2202 = 0.0%, p = fatal and nc 4687 3756 3474 1113 = 0.0%, p = fatal and nc fatal and nc | 4687 2333 5795 4347 8582 8578 2202 2199 = 0.0%, p = 0.477) n 4687 2333 3756 2900 3474 3500 1113 1107 = 0.0%, p = 0.813) 2039 2039 1447 5108 5078 1089 1092 = 57.6%, p = 0.094) 4687 2333 3756 2900 3474 3500 1113 1107 = 59.6%, p = 0.017) n 4687 2333 3756 2900 3474 3500 1113 1107 = 59.6%, p = 0.060) 2039 2039 1447 5108 5078 2020 2199 = 0.0%, p = 0.996) n n 4687 2333 3756 2900 3474 3500 1113 1107 = 0.0%, p = 0.937) <t< td=""><td>4687 2333 5795 4347 882 8578 2202 2199 200%, $p = 0.477$) \bullet her 2333 3756 2900 2039 1447 5108 5078 1089 1092 $= 70.7\%$, $p = 0.094$) \bullet 4687 2333 5795 4347 8682 8578 22022 2199 $= 70.7\%$, $p = 0.017$) \bullet n 4687 2333 3756 2900 \bullet 3474 3500 \bullet 1113 1107 \bullet 57.6%, $p = 0.017$) \bullet \bullet n 4687 2333 \bullet 576 578 \bullet \bullet 1113 1107 \bullet \bullet 2039 1447 \bullet \bullet 61687 2333 \bullet \bullet 7766 2900</td></t<> | 4687 2333 5795 4347 882 8578 2202 2199 200% , $p = 0.477$) \bullet her 2333 3756 2900 2039 1447 5108 5078 1089 1092 $= 70.7\%$, $p = 0.094$) \bullet 4687 2333 5795 4347 8682 8578 22022 2199 $= 70.7\%$, $p = 0.017$) \bullet n 4687 2333 3756 2900 \bullet 3474 3500 \bullet 1113 1107 \bullet 57.6% , $p = 0.017$) \bullet \bullet n 4687 2333 \bullet 576 578 \bullet \bullet 1113 1107 \bullet \bullet 2039 1447 \bullet \bullet 61687 2333 \bullet \bullet 7766 2900 |

Figure S2B. Effects of SGLT2 inhibition on HF hospitalization, CV death/HF hospitalization and all cause mortality for patients with (secondary prevention) and without (primary prevention) cardiovascular disease at baseline

| STUDY Inter HF hospitalization | rvention (n | , | | Hazard Ratio (95% CI) |
|-----------------------------------|-------------|------------|-----------------------|--------------------------------------|
| Overall | | | | |
| EMPA-REG | 4687 | 2333 | | 0.65 (0.50, 0.85 |
| CANVAS | 5795 | 4347 | | 0.67 (0.52, 0.87 |
| DECLARE-TIMI | 8582 | 8578 | | 0.73 (0.61, 0.88 |
| CREDENCE | 2202 | 2199 | | |
| Subtotal (I-squared | | | | 0.61 (0.47, 0.80 0.68 (0.60, 0.76 |
| Subtotal (I-Squared | = 0.0%, p | - 0.720) | \sim | 0.00 (0.00, 0.70 |
| Secondary prevention | on | | | |
| EMPA-REG | 4687 | 2333 | _ | 0.65 (0.50, 0.85 |
| CANVAS | 3756 | 2900 | _ | 0.68 (0.51, 0.90 |
| DECLARE-TIMI | 3474 | 3500 | | 0.78 (0.63, 0.97 |
| CREDENCE | 1113 | 1107 | | 0.61 (0.44, 0.84 |
| Subtotal (I-squared | = 0.0%, p | | \diamond | 0.69 (0.61, 0.79 |
| Primary prevention | | | | |
| CANVAS | 2039 | 1447 | e | 0.64 (0.35, 1.15 |
| DECLARE-TIMI | 5108 | 5078 | | 0.64 (0.46, 0.88 |
| CREDENCE | 1089 | 1092 | | 0.61 (0.38, 0.95 |
| Subtotal (I-squared | | | \sim | 0.63 (0.50, 0.80 |
| CV death/ HF hospitali | 080 | | | C2 6 |
| Overall | | | _ [| |
| EMPA-REG | 4687 | 2333 | | 0.66 (0.55, 0.79 |
| CANVAS | 5795 | 4347 | | 0.78 (0.67, 0.91 |
| DECLARE-TIMI | 8582 | 8578 | | 0.83 (0.73, 0.95 |
| CREDENCE | 2202 | 2199 | | 0.69 (0.57, 0.83 |
| Subtotal (I-squared | | | \diamond | 0.76 (0.70, 0.82 |
| _ | | | | |
| Secondary prevention EMPA-REG | | 0000 | | 0.66 /0 EE 0.70 |
| | 4687 | 2333 | | 0.66 (0.55, 0.79 |
| CANVAS | 3756 | 2900 | | 0.77 (0.65, 0.92 |
| DECLARE-TIMI | 3474 | 3500 | | 0.83 (0.71, 0.98 |
| CREDENCE | 1113 | 1107 | | 0.66 (0.52, 0.83 |
| Subtotal (I-squared | = 34.8%, | o = 0.203) | \diamond | 0.74 (0.68, 0.81 |
| Primary prevention | | | | |
| CANVAS | 2039 | 1447 | _ | 0.83 (0.58, 1.19 |
| DECLARE-TIMI | 5108 | 5078 | | 0.84 (0.67, 1.04 |
| CREDENCE | 1089 | 1092 | | |
| Subtotal (I-squared | | | \sim | 0.74 (0.53, 1.02 0.81 (0.69, 0.96 |
| All Cause Mortality | 0107010 | 0.010) | ~ | 0.01 (0.00) 0.00 |
| Overall | | | _ 1 | |
| EMPA-REG | 4687 | 2333 | | 0.68 (0.57, 0.82 |
| CANVAS | 5795 | 4347 | | 0.87 (0.74, 1.01 |
| DECLARE-TIMI | 8582 | 8578 | | 0.93 (0.82, 1.04 |
| CREDENCE | 2202 | 2199 | | 0.83 (0.68, 1.02 |
| Subtotal (I-squared | = 63.1%, p | o = 0.044) | \diamond | 0.85 (0.79, 0.92 |
| Secondary preventio | on | | | |
| EMPA-REG | 4687 | 2333 | | 0.68 (0.57, 0.82 |
| CANVAS | 3756 | 2900 | | 0.89 (0.75, 1.07 |
| DECLARE-TIMI | 3474 | 3500 | | 0.92 (0.79, 1.08 |
| CREDENCE | 1113 | 1107 | | 0.79 (0.61, 1.02 |
| Subtotal (I-squared | = 57.2%, p | o = 0.071) | \diamond | 0.83 (0.75, 0.94 |
| Primary prevention | | | | |
| CANVAS | 2039 | 1447 | _ _ | 0.79 (0.58, 1.07 |
| DECLARE-TIMI | 5108 | 5078 | | 0.94 (0.78, 1.12 |
| CREDENCE | 1089 | 1092 | | 0.89 (0.63, 1.26 |
| Subtotal (I-squared | | | $\overline{\diamond}$ | 0.90 (0.78, 1.03 |
| | | | | |
| | | | | |

Figure S2C. Effects of SGLT2 inhibition on non-fatal MI and stroke for patients with (secondary prevention) and without (primary prevention) cardiovascular disease at baseline

| STUDY I Non-fatal Myoca | | n (n) Placebo (n) | | Hazard Ratio (95% C |
|------------------------------------|---------------|-------------------|-------------------|---------------------|
| Overall | ruiai iiiare | | | |
| EMPA-REG | 4687 | 2333 | | 0.87 (0.70, 1.09) |
| CANVAS | 5795 | 4347 | | 0.85 (0.69, 1.05) |
| CREDENCE | 2202 | 2199 | | 0.81 (0.59, 1.10) |
| Subtotal (I-squar | red = 0.0%, j | o = 0.935) | \diamond | 0.85 (0.74, 0.97) |
| Secondary preve | ntion | | | |
| EMPA-REG | 4687 | 2333 | | 0.87 (0.70, 1.09) |
| CANVAS | 3756 | 2900 | | 0.79 (0.63, 0.99) |
| CREDENCE | 1113 | 1107 | | 0.91 (0.63, 1.31) |
| Subtotal (I-squar | red = 0.0%, | o = 0.755) | \diamond | 0.84 (0.73, 0.97) |
| Primary prevention | on | | | |
| CANVAS | 2039 | 1447 | _ | 1.21 (0.73, 2.00) |
| CREDENCE | 1089 | 1092 | | 0.57 (0.30, 1.04) |
| Subtotal (I-squar | red = 70.6%, | p = 0.065) | $\langle \rangle$ | 0.90 (0.61, 1.33) |
| lon-fatal Stroke Overall | | | | |
| EMPA-REG | 4687 | 2333 | | 1.24 (0.92, 1.67 |
| CANVAS | 5795 | 4347 | | 0.90 (0.71, 1.15 |
| CREDENCE | 2202 | 2199 | | 0.80 (0.55, 1.14 |
| Subtotal (I-square | d = 50.6%, | o = 0.132) | \diamond | 0.97 (0.82, 1.15 |
| Secondary preven | tion | | | |
| EMPA-REG | 4687 | 2333 | | 1.24 (0.92, 1.67 |
| CANVAS | 3756 | 2900 | | 0.88 (0.67, 1.16 |
| CREDENCE | 1113 | 1107 | _ | 0.97 (0.62, 1.50 |
| Subtotal (I-square | d = 28.8%, | o = 0.245) | \diamond | 1.02 (0.85, 1.22 |
| Primary preventior | ı | | | |
| CANVAS | 2039 | 1447 | | 0.97 (0.59, 1.61 |
| CREDENCE | 1089 | 1092 | | 0.54 (0.27, 1.01 |
| Subtotal (I-square | d = 47.9%, | p = 0.166) | \frown | 0.78 (0.52, 1.17 |
| | | | | |
| | | .25 | .5 1 2 | 1 |

Figure S3A. Effects of SGLT2 inhibition on MACE, CV death, total MI and total stroke for patient with (estimated glomerular filtration rate <60mls/min/1.73m²) and without (estimated glomerular filtration rate >60mls/min/1.73m²) reduced kidney function at baseline, for each included study

| Major Adverse Cardia | c Event | | | | |
|-----------------------------------|------------------|---------------|--------------|----------|------------------------------------|
| Overall | | | | | |
| EMPA-REG | | 333 | | 1 | 0.86 (0.74, 0.9 |
| CANVAS | | 347 | | | 0.86 (0.75, 0.9 |
| | | 578 199 | | 1 | 0.93 (0.84, 1.0 |
| CREDENCE Subtotal (I-squared | | | \diamond | | 0.88 (0.82, 0.9 |
| eGFR<60 at baselin | e | | | | |
| EMPA-REG CANVAS | | 07 29 | | - | 0.88 (0.69, 1.1 0.70 (0.55, 0.9 |
| | | 59 | | | 0.92 (0.69, 1.2 |
| CREDENCE | 1308 1 | 323 | - | | 0.75 (0.60, 0.9 |
| Subtotal (I-squared | | .405) | \checkmark | | 0.80 (0.70, 0.9 |
| GFR>60 at baselin EMPA-REG | | 726 | | - | 0.84 (0.70, 1.0 |
| CANVAS | | 417 | | <u>+</u> | 0.92 (0.79, 1.0 |
| | | 919 | - | - | 0.95 (0.85, 1.0 |
| CREDENCE Subtotal (I-squared | | 76 .724) | | | 0.90 (0.66, 1.2 0.92 (0.85, 0.9 |
| CV Death | | | | | |
| Overall | 1007 0 | 222 | | | 0.00 (0.10.0.7 |
| EMPA-REG | | 333 | | | 0.62 (0.49, 0.7 |
| CANVAS | | 347 | | I | 0.87 (0.72, 1.0 |
| DECLARE-TIMI | 8582 8 | 578 | | - | 0.98 (0.82, 1.1 |
| CREDENCE | 2202 2 | 199 | | - | 0.78 (0.61, 1.0 |
| Subtotal (I-squared | = 70.7%, p = | 0.017) | \diamond | | 0.83 (0.75, 0.9 |
| GFR<60 at baselin | e | | | | |
| EMPA-REG | | 07 | | + | 0.78 (0.54, 1.1 |
| CANVAS | | 29 | | <u> </u> | 0.96 (0.69, 1.3 |
| | | 59 | | <u> </u> | 0.90 (0.57, 1.4 |
| CREDENCE | | 323 | | | 0.74 (0.54, 1.0 |
| Subtotal (I-squared | | | \diamond | - | 0.83 (0.70, 0.9 |
| | | | | | |
| GFR>60 at baselin EMPA-REG | | 726 | | | 0.53 (0.40, 0.7 |
| CANVAS | | 417 | _ | L. | 0.84 (0.67, 1.0 |
| | | | | | |
| DECLARE-TIMI | | 919 | | | 1.00 (0.81, 1.2 |
| CREDENCE | | 76 | - | | 0.87 (0.56, 1.3 |
| Subtotal (I-squared | = 76.8%, p = | 0.005) | \diamond | | 0.83 (0.73, 0.9 |
| Ayocardial Infarction | (fatal and non-f | 'atal) | | | |
| Verall EMPA-REG | 4687 2 | 333 | | | 0.87 (0.70 4.0 |
| | | 333 | | | 0.87 (0.70, 1.0 |
| CANVAS | | 347 | | | 0.89 (0.73, 1.0 |
| | | 578 | | | 0.89 (0.77, 1.0 |
| CREDENCE Subtotal (I-squared | | 199 .996) | | | 0.86 (0.64, 1.1 0.88 (0.80, 0.9 |
| | | | ~ | | |
| GFR<60 at baselin EMPA-REG | | 07 | | | 0 07 /0 67 4 4 |
| | | | | | 0.97 (0.67, 1.4 |
| CANVAS | | 29 | | | 0.62 (0.41, 0.9 |
| | | 59 | | | 0.88 (0.58, 1.3 |
| CREDENCE Subtotal (I-squared | | 323 .426) | | | 0.80 (0.56, 1.1 0.81 (0.67, 0.9 |
| | | / | \sim | | 0.0.1 (0.01, 0.0 |
| GFR>60 at baselin EMPA-REG | | 726 | | L | 0.83 (0.63, 1.0 |
| CANVAS | | 417 | | | |
| | | | | | 1.01 (0.80, 1.2 |
| | | 919 | | I a | 0.89 (0.76, 1.0 |
| CREDENCE Subtotal (I-squared | | 76 688) | | | 1.00 (0.60, 1.6 0.91 (0.82, 1.0 |
| | | | \sim | | 0.01 (0.02, 1.0 |
| troke (fatal and non-f overall | atal) | | | | |
| EMPA-REG | 4687 23 | 333 | _ | | 1.18 (0.89, 1.5 |
| CANVAS | | 347 | | +- | 0.87 (0.69, 1.0 |
| DECLARE-TIMI | 8582 8 | 578 | 7 | | 1.01 (0.84, 1.2 |
| | | 199 | | Ę | 0.77 (0.55, 1.0 |
| Subtotal (I-squared | | 0.109) | < | T | 0.96 (0.86, 1.0 |
| GFR<60 at baselin EMPA-REG | | 07 | | | 0.92 (0.58, 1.4 |
| CANVAS | 1110 93 | 29 — | _ | | 0.50 (0.30, 0.8 |
| | | 59 | _ | | 1.23 (0.70, 2.1 |
| CREDENCE Subtotal (I-squared | | 323 0.078) | | | 0.63 (0.40, 0.9 0.75 (0.59, 0.9 |
| | | | | | |
| GFR>60 at baselin EMPA-REG | 3473 1 | 726 | - | | 1.34 (0.94, 1.9 |
| | | 417 | | | 1.01 (0.78, 1.3 |
| | | 919 | - | _ | 0.98 (0.79, 1.1 |
| CREDENCE Subtotal (I-squared | | 76 .497) | < | | 1.10 (0.64, 1.9 1.05 (0.91, 1.2 |
| | | | | | |
| | | | | 1 | |

Figure S3B. Effects of SGLT2 inhibition on HF hospitalization, CV death/HF hospitalization and all cause mortality for patients with (estimated glomerular filtration rate <60mls/min/1.73m²) and without (estimated glomerular filtration rate >60mls/min/1.73m²) reduced kidney function at baseline, for each included study

| 2333 4347 8578 2199 , p = 0.720) | | 0.65 (0.50, 0.85) 0.67 (0.52, 0.87) 0.73 (0.61, 0.88) |
|--|--|---|
| 4347 8578 2199 | | 0.67 (0.52, 0.87) |
| 4347 8578 2199 | | 0.67 (0.52, 0.87) |
| 8578 2199 | | |
| | | |
| , p = 0.720) | \diamond | 0.61 (0.47, 0.80) |
| | | 0.68 (0.60, 0.76) |
| | | |
| 607 | | 0.59 (0.39, 0.88) |
| 929 | | 0.57 (0.38, 0.86) |
| 659 | | 0.70 (0.44, 1.12) |
| 1323 , p = 0.915) | | 0.64 (0.47, 0.88) 0.62 (0.51, 0.75) |
| | | |
| 1726 | _ | 0.70 (0.49, 1.00) |
| 3417 | _ _ | 0.76 (0.55, 1.06) |
| 7919 | | 0.72 (0.58, 0.87) |
| 876 | _ | 0.55 (0.33, 0.89) |
| , p = 0.750) | \diamond | 0.71 (0.61, 0.82) |
| | | |
| 2333 | _ | 0.66 (0.55, 0.79) |
| | | |
| | | 0.78 (0.67, 0.91) |
| | =- | 0.83 (0.73, 0.95) |
| 2199 | ———— | 0.69 (0.57, 0.83) |
| , p = 0.160) | \diamond | 0.76 (0.70, 0.82) |
| | | |
| 929 | | 0.75 (0.57, 0.98) |
| | | |
| | | 0.78 (0.55, 1.09) |
| | ~ | 0.68 (0.53, 0.85) |
| p = 0.772) | \sim | 0.72 (0.62, 0.85) |
| | _ | |
| 3417 | | 0.81 (0.66, 0.98) |
| 7919 | | 0.84 (0.73, 0.96) |
| 876 | | 0.73 (0.51, 1.02) |
| | \diamond | 0.82 (0.74, 0.91) |
| | | |
| 2222 | | 0.68 (0.57, 0.82 |
| | | 0.87 (0.74, 1.01) |
| | | |
| | | 0.93 (0.82, 1.04) |
| | ~ | 0.83 (0.68, 1.02) 0.85 (0.79, 0.92) |
| .,, | • | |
| 007 | | 0.00 /0.50 / 05 |
| | | 0.80 (0.59, 1.07 |
| | | 0.90 (0.68, 1.18 |
| | | 0.91 (0.67, 1.25 |
| | | 0.76 (0.59, 0.98) |
| , p = 0.757) | \diamond | 0.83 (0.72, 0.96 |
| | | |
| | — — — | 0.62 (0.49, 0.78 |
| 3417 | | 0.87 (0.72, 1.04) |
| 7919 | | 0.93 (0.81, 1.05 |
| 876 | | 0.98 (0.69, 1.40) |
| %, p = 0.023) | \diamond | 0.86 (0.78, 0.94 |
| | | |
| 25 | 5 1 2 | 4 |
| | $\begin{array}{c} 3417\\ 7919\\ 876\\ ,p=0.750) \end{array}$ | 1726 3417 7919 876 2333 4347 8578 2199 929 659 1323 $p = 0.772)$ 3417 7919 876 $p = 0.747)$ 2333 4347 8578 2199 $6, p = 0.044)$ 607 929 659 1323 4347 8578 2199 $6, p = 0.044)$ 607 929 659 1323 4347 8578 2199 $6, p = 0.044)$ 607 929 659 1323 4347 4578 2199 $6, p = 0.023)$ 4 |

Figure S3C. Effects of SGLT2 inhibition on non-fatal MI and stroke for patients with (estimated glomerular filtration rate <60mls/min/1.73m²) and without (estimated glomerular filtration rate >60mls/min/1.73m²) reduced kidney function at baseline, for each included study

| STUDY | Interventio | on (n) Placebo (n) | Hazard Ratio (95% C |
|--------------------|---------------|--------------------|--------------------------|
| Non-fatal Myoca | rdial Infarc | ion | |
| Overall | | | |
| EMPA-REG | 4687 | 2333 — | 0.87 (0.70, 1.09) |
| CANVAS | 5795 | 4347 — | 0.85 (0.69, 1.05) |
| CREDENCE | 2202 | 2199 | 0.81 (0.59, 1.10) |
| Subtotal (I-square | d = 0.0%, p = | 0.935) < | 0.85 (0.74, 0.97) |
| eGFR<60 at basel | ine | | |
| CANVAS | 1110 | 929 | - 0.55 (0.36, 0.85) |
| CREDENCE | 1308 | 1323 ——— | 0.76 (0.52, 1.10) |
| Subtotal (I-square | d = 19.1%, p | = 0.266) | > 0.66 (0.50, 0.88) |
| eGFR>60 at basel | ine | | |
| CANVAS | 4684 | 3417 | 0.99 (0.77, 1.26) |
| CREDENCE | 893 | 876 | 0.92 (0.53, 1.62) |
| Subtotal (I-square | d = 0.0%, p = | 0.823) | 0.98 (0.78, 1.22) |
| Non-fatal Stroke | | | |
| Overall | | | 1 |
| EMPA-REG | 4687 | 2333 | 1.24 (0.92, 1.67) |
| CANVAS | 5795 | 4347 | 0.90 (0.71, 1.15) |
| CREDENCE | 2202 | 2199 | 0.80 (0.55, 1.14) |
| Subtotal (I-square | d = 50.6%, p | = 0.132) | 0.97 (0.82, 1.15) |
| eGFR<60 at basel | ine | | |
| CANVAS | 1110 | 929 | 0.57 (0.33, 0.98) |
| CREDENCE | 1308 | 1323 | 0.69 (0.43, 1.09) |
| Subtotal (I-square | d = 0.0%, p | 0.601) | > 0.64 (0.45, 0.91) |
| eGFR>60 at basel | ine | | |
| CANVAS | 4684 | 3417 | 1.02 (0.77, 1.34) |
| CREDENCE | 893 | 876 | 1.02 (0.57, 1.84) |
| Subtotal (I-square | d = 0.0%, p | 0.998) | 1.02 (0.79, 1.31) |
| | | | |
| | | | 1 2 4 |

Figure S4A. Effects of SGLT2 inhibition on MACE, CV death, total MI and total stroke for patients with and without a history of heart failure at baseline, for each included study

| CANVAS DECLARE-TIMI CREDENCE Subtotal (I-squared = HF at baseline CANVAS DECLARE-TIMI | 4687 5795 8582 2202 | 2333 4347 8578 | 0.86 (0.74, 0.9 0.86 (0.75, 0.9 |
|---|------------------------------|----------------------|---|
| EMPA-REG CANVAS DECLARE-TIMI CREDENCE Subtotal (I-squared = HF at baseline CANVAS DECLARE-TIMI | 5795 8582 2202 | 4347 | |
| CANVAS DECLARE-TIMI CREDENCE Subtotal (I-squared = HF at baseline CANVAS DECLARE-TIMI | 5795 8582 2202 | 4347 | |
| DECLARE-TIMI CREDENCE Subtotal (I-squared = HF at baseline CANVAS DECLARE-TIMI | 8582 2202 | | |
| CREDENCE Subtotal (I-squared = HF at baseline CANVAS DECLARE-TIMI | 2202 | 0010 | - 0.93 (0.84, 1.0 |
| Subtotal (I-squared = HF at baseline CANVAS DECLARE-TIMI | | 2100 | |
| HF at baseline CANVAS DECLARE-TIMI | 0.0%, p = 0 | 2199 0.477) | 0.80 (0.67, 0.9 0.88 (0.82, 0.9 |
| CANVAS DECLARE-TIMI | 0.070, p = 1 | | V 0.00 (0.02, 0.0 |
| DECLARE-TIMI | 803 | 658 | 0.80 (0.61, 1.0 |
| | | | — |
| CREDENCE | 852 | 872 | 1.01 (0.81, 1.2 |
| Subtotal (I-squared = | 329 0.0%, p = (| 323 0.431) | 0.93 (0.63, 1.3 0.92 (0.79, 1.0 |
| | | | |
| No HF at baseline CANVAS | 4992 | 3689 | 0.87 (0.76, 1.0 |
| | 7730 | 7706 | |
| | 1873 | 1876 | |
| Subtotal (I-squared = | | | 0.76 (0.62, 0.9 0.88 (0.81, 0.9 |
| | | | ~ · · · · · · · · · · · · · · · · · · · |
| CV Death Overall | | | |
| | 4687 | 2333 | 0.62 (0.49, 0.7 |
| CANVAS | 5795 | 4347 | 0.87 (0.72, 1.0 |
| DECLARE-TIMI | 8582 | 8578 | 0.98 (0.82, 1.1 |
| | 2202 | 2199 | 0.78 (0.61, 1.0 |
| Subtotal (I-squared | | = 0.017) | 0.83 (0.75, 0.9 |
| HF at baseline | | | |
| | 462 | 244 | 0.71 (0.43, 1.1 |
| | 803 | 658 | 0.72 (0.51, 1.0 |
| | 852 | 872 | 1.01 (0.73, 1.3 |
| CREDENCE | 329 | 323 | 1.02 (0.63, 1.6 |
| Subtotal (I-squared | = 0.8%, p = | = 0.388) | 0.86 (0.71, 1.0 |
| No HF at baseline | | | |
| EMPA-REG | 4225 | 2089 | 0.60 (0.47, 0.7 |
| CANVAS | 4992 | 3689 | 0.95 (0.76, 1.2 |
| DECLARE-TIMI | 7730 | 7706 | 0.97 (0.78, 1.2 |
| CREDENCE | 1873 | 1876 | 0.70 (0.52, 0.9 |
| Subtotal (I-squared | = 73.1%, p | = 0.011) | 0.81 (0.72, 0.9 |
| Myocardial Infarction (f | atal and nor | ı-fatal) | |
| Overall EMPA-REG | 4687 | 2333 | 0.87 (0.70, 1.09 |
| | 5795 | 4347 | 0.89 (0.73, 1.05 |
| | | | |
| | 8582 | 8578 | |
| | 2202 | 2199 | 0.86 (0.64, 1.16 |
| Subtotal (I-squared = | 0.0%, p = (| 0.996) | 0.88 (0.80, 0.97 |
| HF at baseline | | | |
| | 803 | 658 | 1.11 (0.65, 1.89 |
| DECLARE-TIMI | 852 | 872 | 0.85 (0.61, 1.18 |
| | 329 | 323 | 1.79 (0.85, 4.02 |
| Subtotal (I-squared = | 38.1%, p = | 0.199) | 0.99 (0.76, 1.29 |
| No HF at baseline | | | |
| CANVAS | 4992 | 3689 | 0.86 (0.69, 1.06 |
| DECLARE-TIMI | 7730 | 7706 | |
| CREDENCE | 1873 | 1876 | 0.75 (0.54, 1.04 |
| Subtotal (I-squared = | 0.0%, p = | 0.648) | 0.86 (0.77, 0.97 |
| troke (fatal and non-fa | tal) | | |
| Overall | 1697 | 2222 | |
| | 4687 | 2333 | 1.18 (0.89, 1.5 |
| | 5795 | 4347 | 0.87 (0.69, 1.0 |
| | 3582 | 8578 | |
| | 2202 | 2199 | 0.77 (0.55, 1.0 |
| Subtotal (I-squared = | 37.1%, p = | 0.189) | 0.96 (0.86, 1.0 |
| HF at baseline | | | |
| | 303 | 658 | 0.84 (0.51, 1.3 |
| | 352 | 872 | 1.21 (0.77, 1.9 |
| CREDENCE 3 Subtotal (I-squared = | 329 29.4%, p = | 323 0.243) | 0.59 (0.27, 1.2 0.94 (0.69, 1.2 |
| | | | 0.01 (0.00) 1.2 |
| No HF at baseline CANVAS 4 | 4992 | 3689 | 0.88 (0.68, 1.1 |
| | 1992 7730 | 7706 | |
| | | | |
| CREDENCE 1 Subtotal (I-squared = | 1873 0.0%, p = 0 | 1876 0.677) | 0.83 (0.57, 1.2 0.92 (0.80, 1.0 |
| 213 B | 1996 | <i></i> | |
| | | | |

Figure S4B. Effects of SGLT2 inhibition on HF hospitalization, CV death/HF hospitalization and all cause mortality for patients with and without a history of heart failure at baseline, for each included study

| | vention (i | Placebo (n) | Hazard Ratio (95% C |
|----------------------------------|------------------|--|--------------------------------------|
| HF hospitalization | | | |
| EMPA-REG | 4687 | 2333 | 0.65 (0.50, 0.85 |
| CANVAS | 5795 | 4347 | 0.67 (0.52, 0.87 |
| DECLARE-TIMI | 8582 | 8578 | 0.73 (0.61, 0.88 |
| CREDENCE | 2202 | 2199 | 0.61 (0.47, 0.80 |
| Subtotal (I-squared | | - | 0.68 (0.60, 0.76 |
| Subtotal (I-squared | - 0.0 /0, p | ······································ | 0.00 (0.00, 0.10 |
| HF at baseline EMPA-REG | 462 | 244 | 0.75 /0.49 1.10 |
| | 803 | 658 | 0.75 (0.48, 1.19 0.51 (0.33, 0.78 |
| CANVAS | | | |
| DECLARE-TIMI | 852 | 872 | 0.73 (0.55, 0.96 |
| CREDENCE Subtotal (I-squared | 329 = 0.0%, p | 323 = 0.505) | 0.76 (0.47, 1.22 0.69 (0.57, 0.83 |
| No HF at baseline | | | |
| EMPA-REG | 4225 | 2089 | 0.59 (0.43, 0.82 |
| CANVAS | 4992 | 3689 | 0.39 (0.43, 0.82 |
| DECLARE-TIMI | 7730 | 7706 | • |
| CREDENCE | 1873 | 1876 | 0.73 (0.58, 0.92 0.54 (0.39, 0.75 |
| Subtotal (I-squared | | ~ | 0.67 (0.58, 0.77 |
| V death/ HF bosnital | ization | | |
| CV death/ HF hospital Overall | 12811011 | | |
| EMPA-REG | 4687 | 2333 — | 0.66 (0.55, 0.79 |
| CANVAS | 5795 | 4347 | 0.78 (0.67, 0.91 |
| DECLARE-TIMI | 8582 | 8578 | 0.83 (0.73, 0.95 |
| CREDENCE | 2202 | 2199 - | • |
| | | | 0.69 (0.57, 0.83 |
| Subtotal (I-squared | = 41.9%, | = 0.160) | 0.76 (0.70, 0.82 |
| IF at baseline | | | |
| EMPA-REG | 462 | 244 | 0.72 (0.50, 1.04 |
| CANVAS | 803 | 658 | 0.61 (0.46, 0.80 |
| DECLARE-TIMI | 852 | 872 | - 0.79 (0.63, 0.99 |
| CREDENCE | 329 | 323 | 0.82 (0.57, 1.19 |
| Subtotal (I-squared | = 0.0%, p | = 0.480) | 0.73 (0.63, 0.84 |
| No HF at baseline | | | |
| EMPA-REG | 4225 | 2089 | 0.63 (0.51, 0.78 |
| CANVAS | 4992 | 3689 | 0.87 (0.72, 1.06 |
| DECLARE-TIMI | 7730 | 7706 | - 0.84 (0.72, 0.99 |
| CREDENCE | 1873 | 1876 | 0.64 (0.51, 0.80 |
| Subtotal (I-squared | = 65.2%, | = 0.035) | 0.76 (0.69, 0.84 |
| All Cause Mortality | | | |
| Overall | | - | |
| EMPA-REG | 4687 | 2333 — | 0.68 (0.57, 0.82 |
| CANVAS | 5795 | 4347 | 0.87 (0.74, 1.0 |
| DECLARE-TIMI | 8582 | 8578 — | 0.93 (0.82, 1.04 |
| CREDENCE | 2202 | 2199 | 0.83 (0.68, 1.02 |
| Subtotal (I-squared | | A | 0.85 (0.79, 0.92 |
| IF at baseline | | | |
| | 460 | 244 | 0.70 /0.50 4.00 |
| EMPA-REG | 462 | 244 | 0.79 (0.52, 1.20 |
| CANVAS | 803 | 658 | 0.70 (0.51, 0.96 |
| DECLARE-TIMI | 852 | 872 | 0.87 (0.68, 1.12 |
| CREDENCE | 329 | 323 | 0.94 (0.62, 1.43 |
| Subtotal (I-squared | = 0.0%, p | = 0.655) | 0.82 (0.69, 0.96 |
| lo HF at baseline | | | |
| EMPA-REG | 4225 | 2089 | 0.66 (0.51, 0.81 |
| | | | |
| CANVAS | 4992 | 3689 — | 0.93 (0.78, 1.11 |
| DECLARE-TIMI | 7730 | 7706 — | 0.94 (0.82, 1.07 |
| CREDENCE | 1873 | 1876 | 0.79 (0.62, 1.00 |
| Subtotal (I-squared | = 62.3%, | = 0.047) | 0.87 (0.79, 0.95 |
| | | | |
| | | | |

Figure S4C. Effects of SGLT2 inhibition on non-fatal MI and stroke for patients with and without a history of heart failure at baseline, for each included study

| STUDY | Interventio | n (n) Placebo (n) | | Hazard Ratio (95% C |
|-----------------------------|----------------|-------------------|-------------------|--------------------------|
| Non-fatal Myocar | rdial Infarcti | ion | | |
| Overall | | | | |
| EMPA-REG | 4687 | 2333 | | 0.87 (0.70, 1.09) |
| CANVAS | 5795 | 4347 | | 0.85 (0.69, 1.05) |
| CREDENCE | 2202 | 2199 | | 0.81 (0.59, 1.10) |
| Subtotal (I-square | d = 0.0%, p = | = 0.935) | \diamond | 0.85 (0.74, 0.97) |
| HF at baseline | | | | |
| CANVAS | 803 | 658 | | 1.39 (0.75, 2.56) |
| CREDENCE | 329 | 323 | | 1.32 (0.59, 3.05) |
| Subtotal (I-square | d = 0.0%, p = | = 0.921) | | 1.36 (0.83, 2.23) |
| No HF at baseline | | | | |
| CANVAS | 4992 | 3689 | | 0.80 (0.64, 1.00) |
| CREDENCE | 1873 | 1876 | | 0.74 (0.52, 1.04) |
| Subtotal (I-square | d = 0.0%, p = | = 0.711) | \diamond | 0.78 (0.65, 0.94) |
| Non-fatal Stroke | | | | |
| Overall | | | | |
| EMPA-REG | 4687 | 2333 | | 1.24 (0.92, 1.67) |
| CANVAS | 5795 | 4347 | | 0.90 (0.71, 1.15) |
| CREDENCE | 2202 | 2199 | | 0.80 (0.55, 1.14) |
| Subtotal (I-square | ed = 50.6%, p | = 0.132) | \diamond | 0.97 (0.82, 1.15) |
| HF at baseline | | | | |
| CANVAS | 803 | 658 | _ | 0.85 (0.49, 1.49) |
| CREDENCE | 329 | 323 | _ | 0.56 (0.22, 1.30) |
| Subtotal (I-square | ed = 0.0%, p = | = 0.435) | $\langle \rangle$ | 0.76 (0.47, 1.21) |
| No HF at baseline | | | | |
| CANVAS | 4992 | 3689 | _ _ | 0.92 (0.70, 1.20) |
| CREDENCE | 1873 | 1876 | _ | 0.86 (0.58, 1.29) |
| Subtotal (I-square | ed = 0.0%, p = | = 0.784) | \sim | 0.90 (0.72, 1.13) |
| - Contraction - Contraction | | | | |
| | | | | |
| | | .25 | .5 1 2 | 4 |

Figure S5. Sensitivity Analysis for the Outcome of Serious Adverse Events without inclusion of Risk Ratios

| Hazard ratio (95% CI) |
|---|
| 0.93 (0.87, 1.00) 0.91 (0.87, 0.96) 0.87 (0.79, 0.97) 0.91 (0.88, 0.94) |
| ■ 0.98 (0.54, 1.77) 0.68 (0.49, 0.95) ■ 1.36 (0.65, 2.91) 0.80 (0.61, 1.05) |
| 2.33 (0.76, 7.17) 2.18 (1.10, 4.30) → 10.80 (1.39, 83.65) 2.50 (1.43, 4.38) |
| ■ 1.26 (1.04, 1.52) 1.04 (0.91, 1.18) 0.98 (0.70, 1.37) 1.09 (0.99, 1.21) |
| − 1.97 (1.41, 2.75) 1.09 (0.84, 1.40) 1.11 (0.79, 1.56) 1.29 (1.08, 1.53) |
| |

Figure S 6. The Effects of SGLT2 inhibition on Major Adverse Cardiac Outcomes for patients depending on Urine Albumin Creatinine Ratio at baseline

| | | | | s/1000 t-years | | | RR (95% CI) | P-heterogeneity |
|-------------------------------------|-------------|----------|-------|-------------------|----------|-----|------------------|-----------------|
| Study | Events | Patients | SGLT2 | Placebo | | | | |
| UACR <30 mg/g | | | | | | | | 0.23 |
| EMPA-REG | 375 | 4171 | 30.6 | 34.5 | | | 0.89 (0.72-1.10) | |
| CANVAS | 596 | 7007 | 22.1 | 26.5 | | | 0.83 (0.71-0.98) | |
| Subtotal (I ² =0.0%, P-h | eterogeneit | y=0.61) | | | • | | 0.85 (0.75-0.97) | |
| UACR 30-300 mg/g | | | | | | | | |
| EMPA-REG | 248 | 2013 | 42.9 | 48.7 | | - | 0.89 (0.69-1.16) | |
| CANVAS | 272 | 2266 | 35.2 | 35.4 | | | 0.98 (0.76-1.25) | |
| Subtotal (I ² =0.0%, P-h | eterogeneit | y=0.60) | | | - | | 0.94 (0.78-1.12) | |
| UACR >300 mg/g | | | | | | | | |
| EMPA-REG | 144 | 769 | 62.2 | 88.9 | e | | 0.69 (0.49-0.96) | |
| CANVAS | 134 | 760 | 53.6 | 72.0 | | | 0.75 (0.53-1.06) | |
| CREDENCE | 486 | 4401 | 38.7 | 48.7 | | | 0.80 (0.67-0.95) | |
| Subtotal (I ² =0.0%, P-h | eterogeneit | y=0.74) | | | • | | 0.77 (0.67-0.89) | |
| | | | | | | | | |
| | | | | 0.3 | 0.5 1 | 1.5 | | |