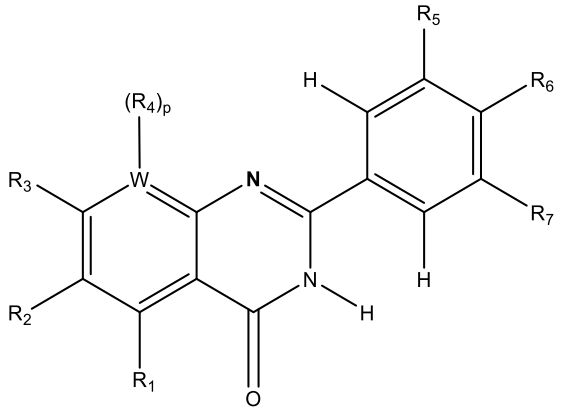
committee -- illustrated a significant reduction of events compared to placebo and SGLT2 inhibitors [HR = 0.40 (95% CI, 0.16 – 1.00; p=0.05)].

Brief Description of the Disclosure

[0009] The present disclosure provides methods of treating and/or preventing Major adverse cardiovascular events (MACE) (including non-fatal myocardial infarction, cardiovascular death, stroke, and hospitalization for CVD events) by administering to a subject in need thereof, a sodium-glucose transport protein 2 (SGLT2) inhibitor and a compound of Formula I or a stereoisomer, tautomer, pharmaceutically acceptable salt, or hydrate thereof.

[0009a] In an aspect, there is provided the use of a sodium-glucose transport protein 2 (SGLT2) inhibitor and a compound of Formula I or a stereoisomer, tautomer, pharmaceutically acceptable salt, or hydrate thereof, wherein:



Formula I

R_1 and R_3 are each independently selected from alkoxy, alkyl, amino, halogen, and hydrogen;

R_2 is selected from alkoxy, alkyl, alkenyl, alkynyl, amide, amino, halogen, and hydrogen;

R_5 and R_7 are each independently selected from alkyl, alkoxy, amino, halogen, and hydrogen;

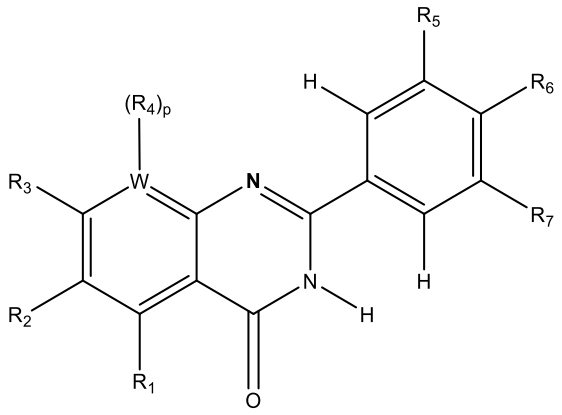
R_6 is selected from amino, amide, alkyl, hydrogen, hydroxyl, piperazinyl, and alkoxy;

W is selected from C and N, wherein if W is N, then p is 0 or 1, and if W is C, then p is 1; and

for W-$(R_4)_p$, W is C, p is 1 and R_4 is H, or W is N and p is 0,

in the manufacture of a medicament for treating and/or preventing major adverse cardiovascular events (MACE) in a subject in need thereof.

[0009b] In another aspect, there is provided the use of a sodium-glucose transport protein 2 (SGLT2) inhibitor and a compound of Formula I or a stereoisomer, tautomer, pharmaceutically acceptable salt, or hydrate thereof, wherein:



Formula I

R_1 and R_3 are each independently selected from alkoxy, alkyl, amino, halogen, and hydrogen;

R_2 is selected from alkoxy, alkyl, alkenyl, alkynyl, amide, amino, halogen, and hydrogen;

R_5 and R_7 are each independently selected from alkyl, alkoxy, amino, halogen, and hydrogen;

R_6 is selected from amino, amide, alkyl, hydrogen, hydroxyl, piperazinyl, and alkoxy;

W is selected from C and N, wherein if W is N, then p is 0 or 1, and if W is C, then p is 1; and

for W-$(R_4)_p$, W is C, p is 1 and R_4 is H, or W is N and p is 0,

in the manufacture of a medicament for treating and/or preventing any individual component of MACE in a subject in need thereof.

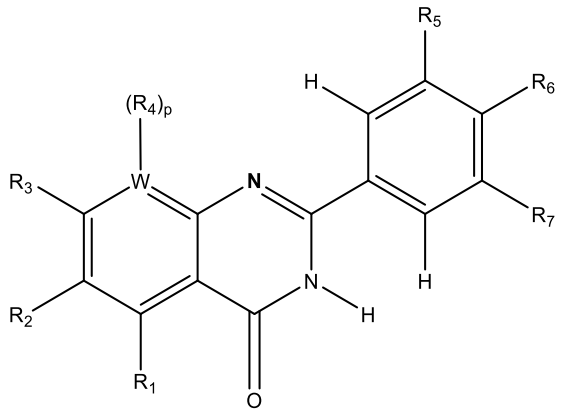
[0010] In some examples, the disclosure provides methods of preventing cardiovascular death by administering to a subject in need thereof, a sodium-glucose transport protein 2 (SGLT2) inhibitor and a compound of Formula I or a stereoisomer, tautomer, pharmaceutically acceptable salt, or hydrate thereof.

[0011] In some examples, the disclosure provides methods of treating and/or preventing hospitalization for CVD events by administering to a subject in need thereof, a sodium-glucose transport protein 2 (SGLT2) inhibitor and a compound of Formula I or a stereoisomer, tautomer, pharmaceutically acceptable salt, or hydrate thereof.

[0012] In some examples, the disclosure provides methods of treating and/or preventing a non-fatal myocardial infarction by administering to a subject in need thereof, a sodium-glucose transport protein 2 (SGLT2) inhibitor and a compound of Formula I or a stereoisomer, tautomer, pharmaceutically acceptable salt, or hydrate thereof.

[0013] In some examples, the compound of Formula I is administered simultaneously with a SGLT2 inhibitor. In some examples, the Compound of Formula I is administered sequentially with the SGLT2 inhibitor. In some examples, the Compound of Formula I is administered in a single pharmaceutical composition with the SGLT2 inhibitor. In some examples, the Compound of Formula I and the SGLT2 inhibitor are administered as separate compositions.

[0014] In some examples, the compound of Formula Ia is selected from



Formula Ia

or a stereoisomer, tautomer, pharmaceutically acceptable salt, or hydrate thereof, wherein:

R_1 and R_3 are each independently selected from alkoxy, alkyl, and hydrogen;

R_2 is selected from alkoxy, alkyl, and hydrogen;

R_5 and R_7 are each independently selected from alkyl, alkoxy, and hydrogen;

R_6 is selected from alkyl, hydroxyl, and alkoxy;

W is selected from C and N, wherein if W is N, then p is 0 or 1, and if W is C, then p is 1; and

for W-$(R_4)_p$, W is C, p is 1 and R_4 is H, or W is N and p is 0.

[0015] In some examples, the Compound of Formula I is 2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)-5,7-dimethoxyquinazolin-4(3H)-one (RVX-208 or RVX000222) or a pharmaceutically acceptable salt thereof.

[0016] In some examples, the SGLT2 inhibitor is empagliflozin, canagliflozin, dapagliflozin, remogliflozin, ipragliflozin, or HM41322. In some examples, the SGLT2 inhibitor is bexagliflozin, ertugliflozin, sotagliflozin, luseogliflozin, or tofogliflozin.

[0017] In some examples, the MACE endpoint is narrowly defined as a single composite endpoint of cardiovascular (CV) death, non-fatal myocardial infarction, or stroke.

[0018] In some examples, the MACE endpoint is broadly defined as a single composite endpoint of cardiovascular (CV) death, non-fatal myocardial infarction, hospitalization for CVD events, or stroke.