

Supplemental Online Content

Colombijn JMT, Idema DL, van Beem S, et al. Representation of patients with chronic kidney disease in clinical trials of cardiovascular disease medications: a systematic review. *JAMA Netw Open*. 2024;7(2):e240427. doi:10.1001/jamanetworkopen.2024.0427

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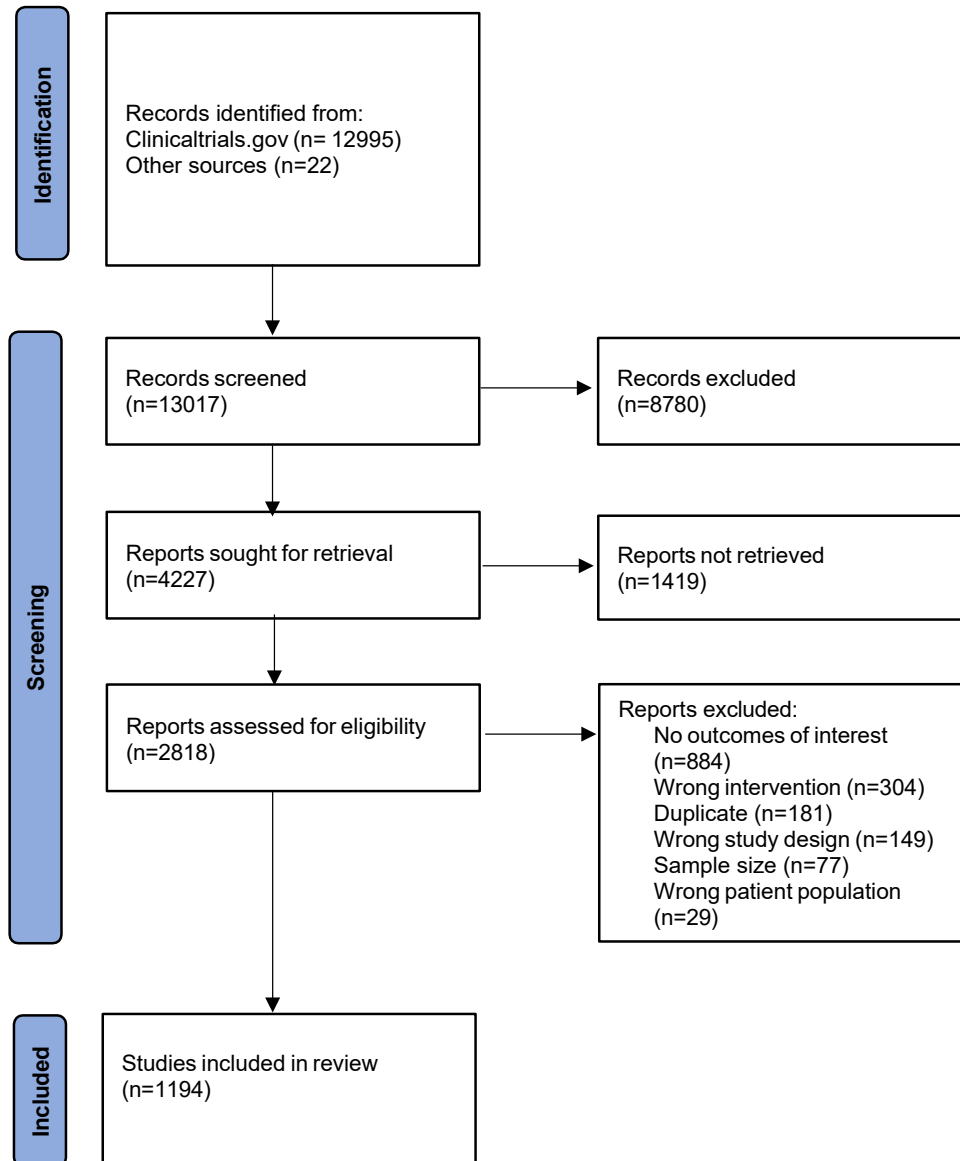
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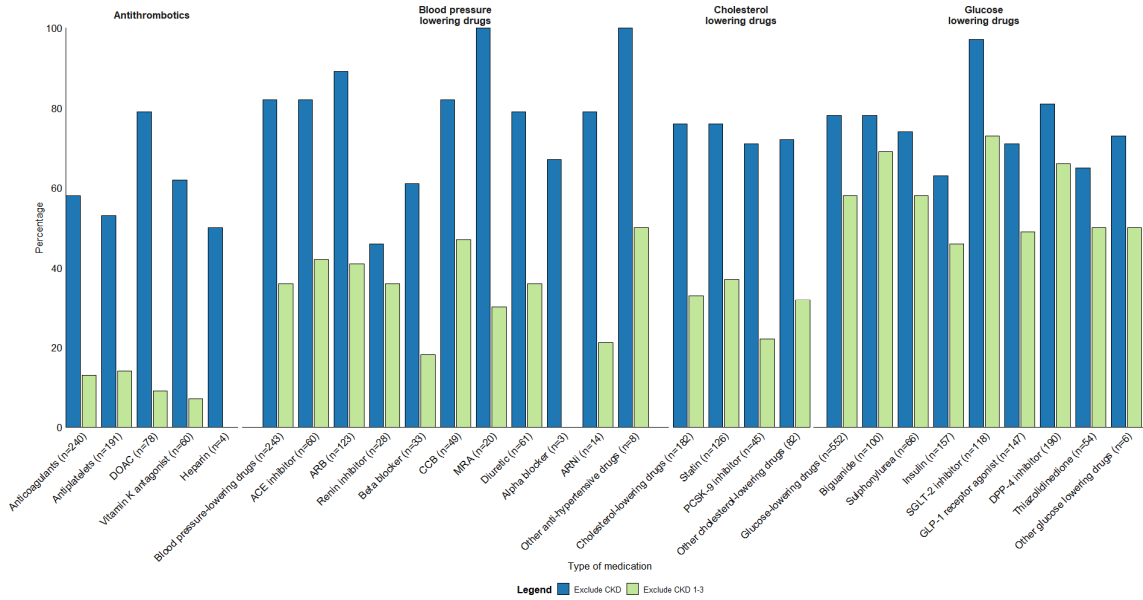
eFigure 12. Heat Map of (Subgroup) Analyses Kidney Failure for People With Different Stages of CKD

This supplemental material has been provided by the authors to give readers additional information about their work.

eFigure 1: Flow chart of literature search.

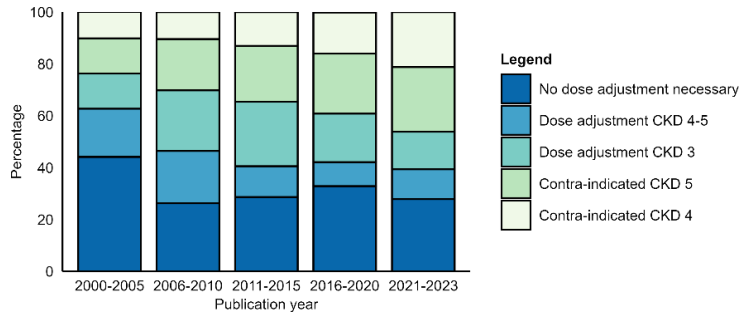


eFigure 2: The exclusion of patients with CKD for different types of cardiovascular medications



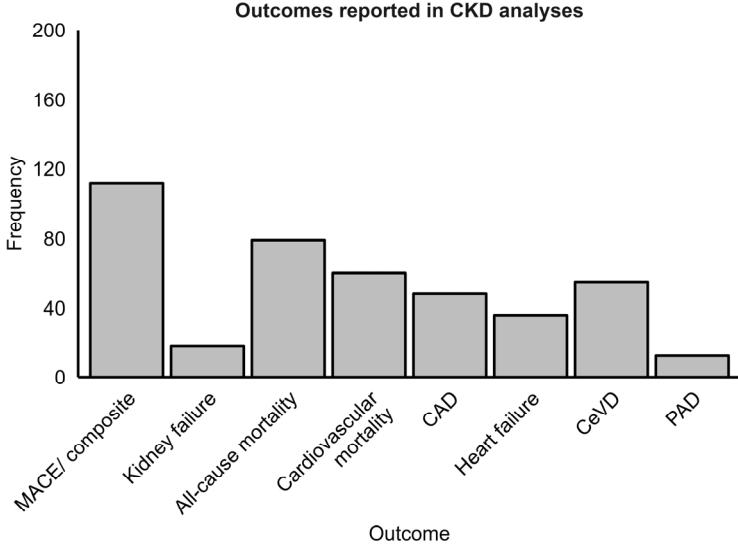
Abbreviations: ACE inhibitor, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; CKD, chronic kidney disease; DOAC, direct oral anticoagulants; DPP-4 receptor agonist, dipeptidyl-peptidase-4 inhibitors; eGFR, estimated glomerular filtration rate; GLP-1 receptor agonist, glucagon-like peptide-1 receptor agonist; MRA, mineralocorticoid receptor antagonist; PCSK-9 inhibitor, proprotein convertase subtilisin/kexin type 9 inhibitor; SCr, serum creatinine; SGLT-2 inhibitor, sodium-glucose cotransporter-2 inhibitor.

eFigure 3: The exclusion of patients with CKD stratified by prescribing recommendations for patients with CKD



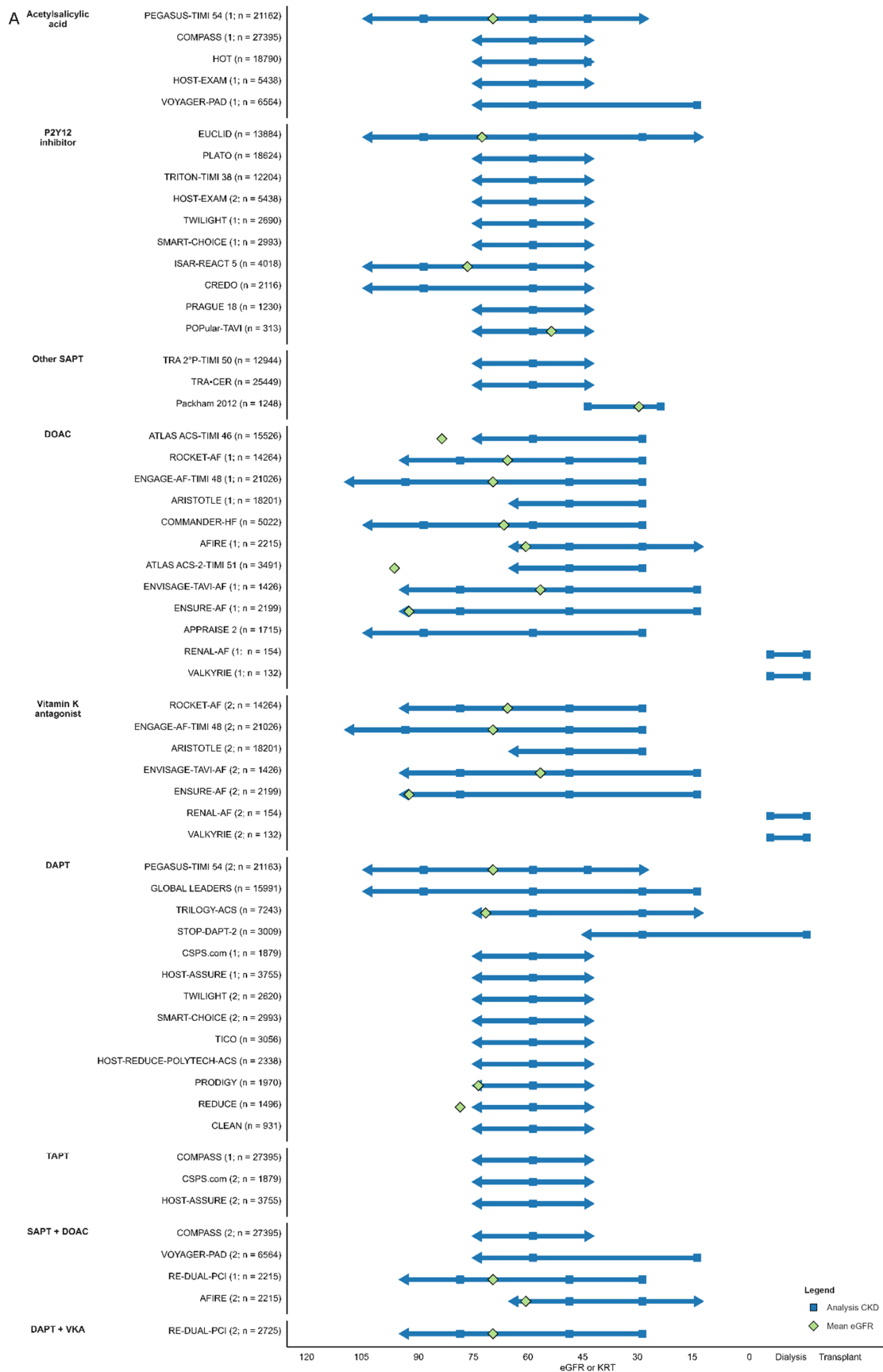
Abbreviations: CKD, chronic kidney disease

Figure 4: the number of analyses for patients with CKD for different cardiovascular outcomes

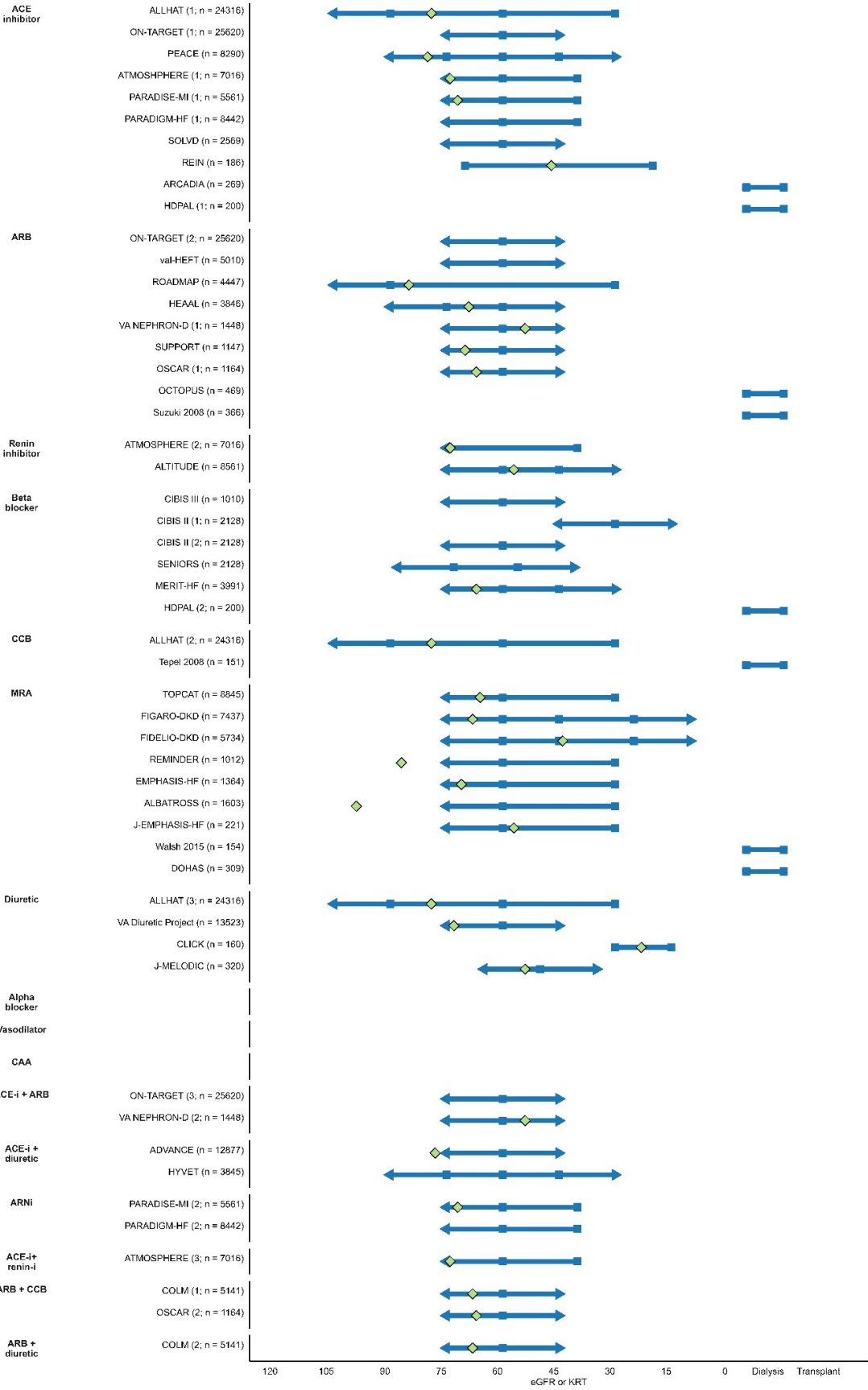


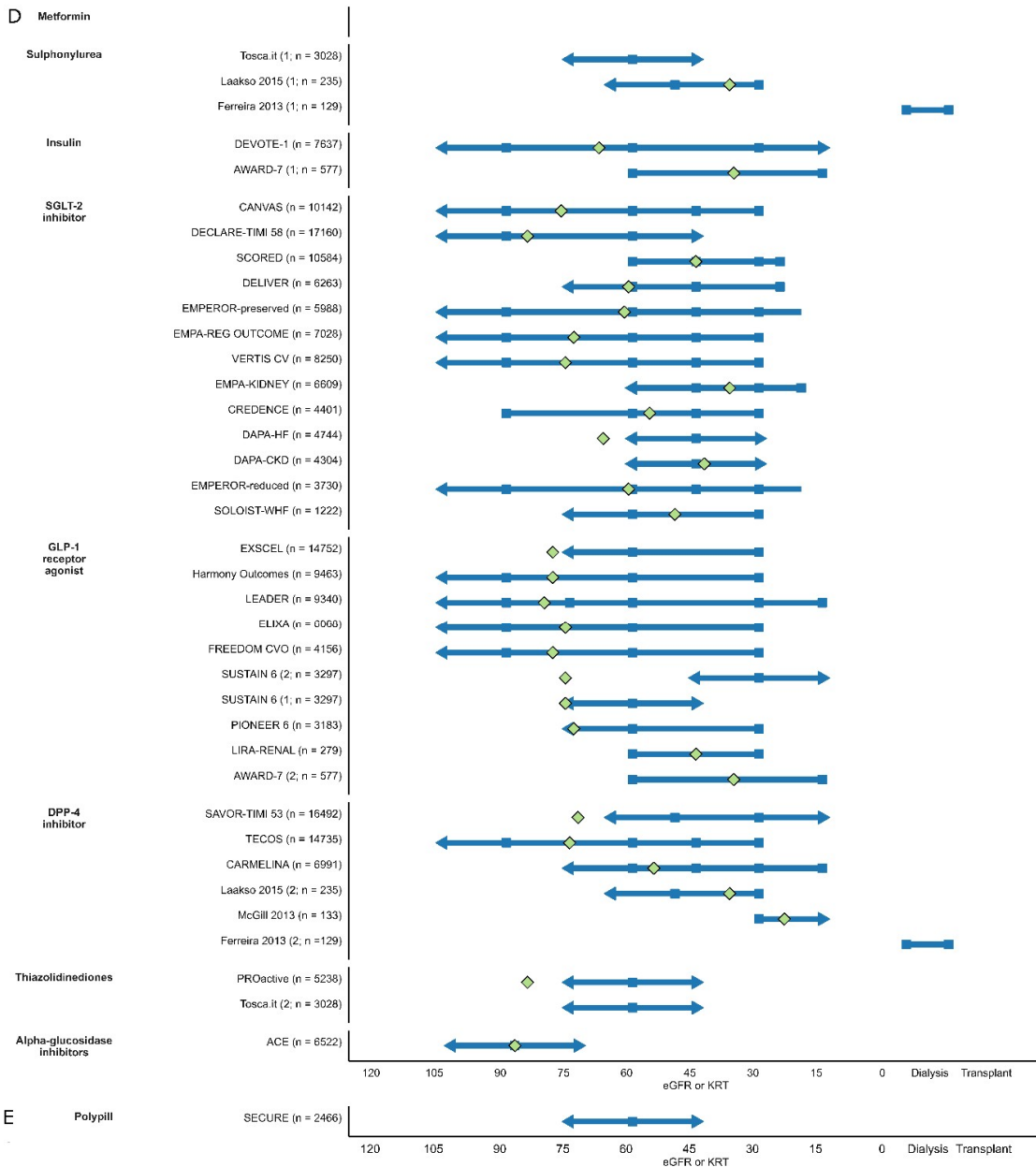
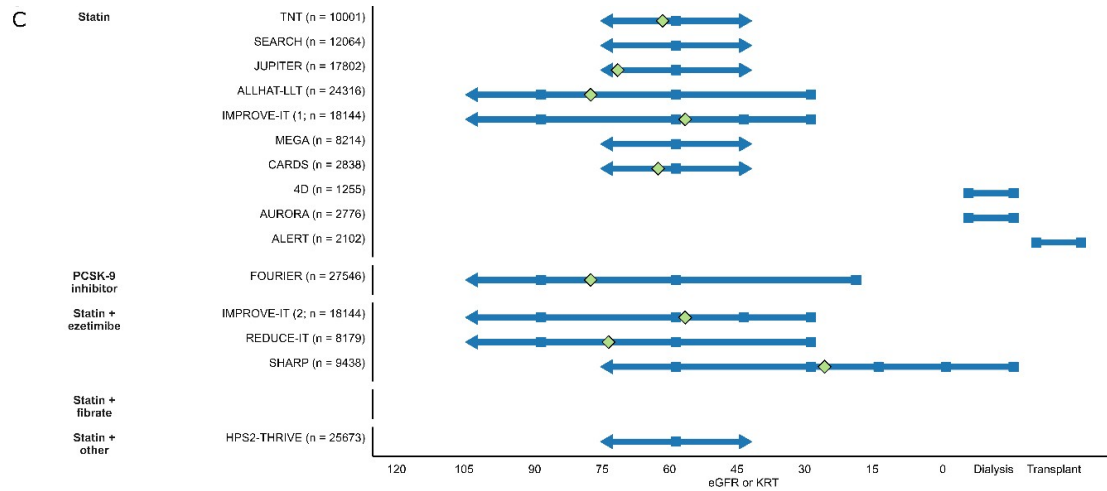
Abbreviations: CAD, coronary artery disease; CeVD, cerebrovascular disease; CKD, chronic kidney disease; MACE, major adverse cardiovascular event; PAD, peripheral arterial disease.

eFigure 5: Overview of individual studies with analysis on eGFR or kidney replacement therapy for major adverse cardiovascular events in patients with CKD. Panel A illustrates analyses for antithrombotics; panel B for blood-pressure-lowering drugs; panel C for cholesterol-lowering drugs; panel D for glucose-lowering drugs; and panel E for polyphills.



B



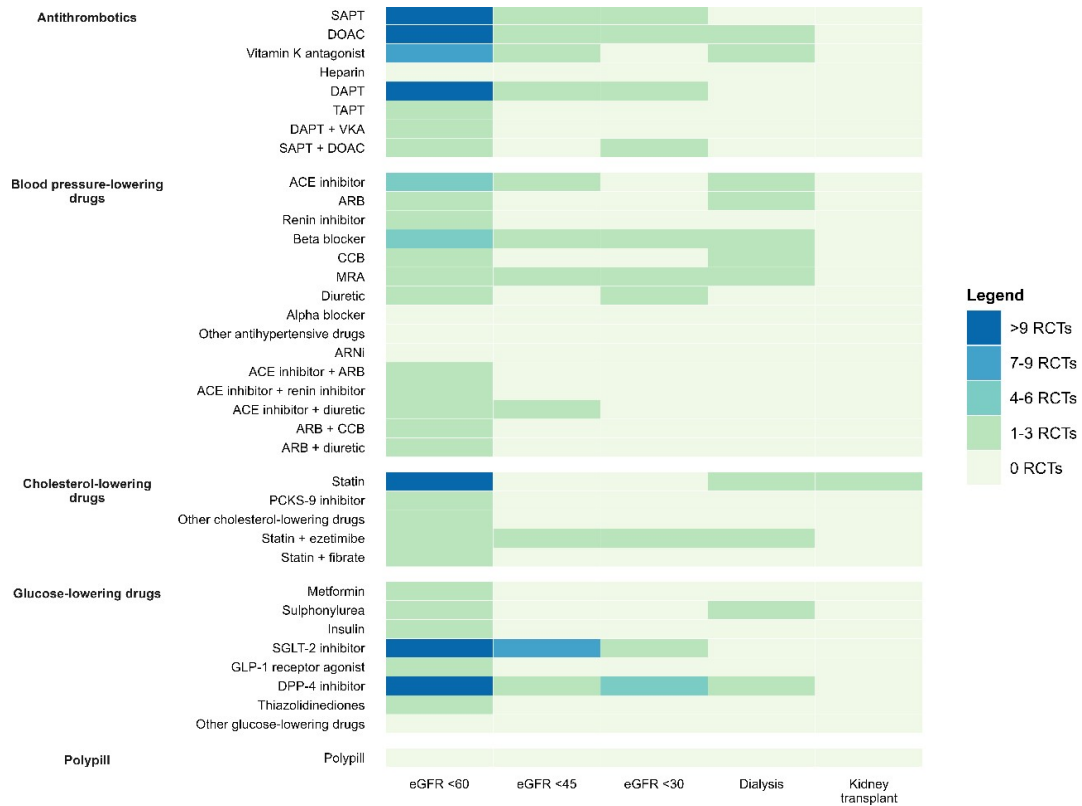


Abbreviations:

ACE-inhibitor/ACE-I, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CAA, centrally-acting antihypertensive; CCB, calcium channel blocker; CKD, chronic kidney disease; DAPT, double antiplatelet therapy; DOAC, direct oral anticoagulants; DPP-4 inhibitor, dipeptidyl-peptidase-4 inhibitor; eGFR, estimated glomerular filtration rate; GLP-1 receptor agonist, glucagon-like peptide-1 receptor agonist; KRT, kidney replacement therapy; MRA, mineralocorticoid receptor antagonist; PCSK-9 inhibitor, proprotein convertase subtilisin/kexin type 9 inhibitor; SAPT, single antiplatelet therapy; SGLT-2 inhibitor, sodium-glucose cotransporter-2 inhibitor; TAPT, triple antiplatelet therapy; VKA, vitamin K antagonist.

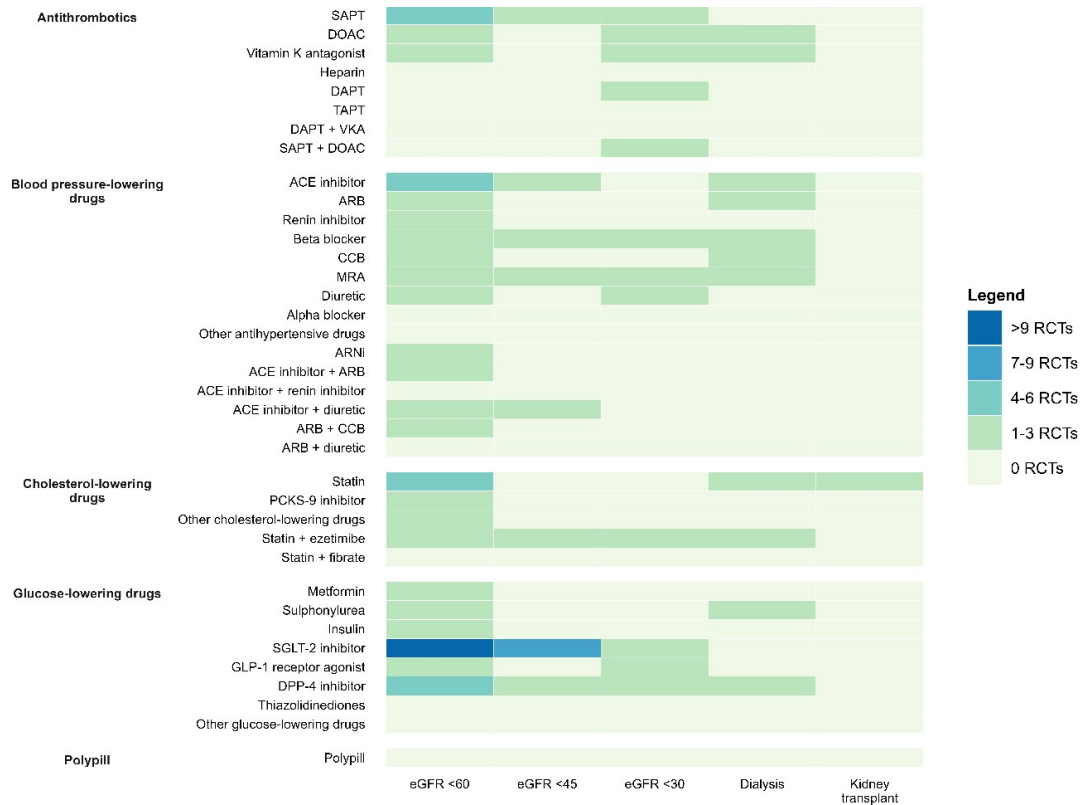
Each line represents a comparison arm in an RCT. Each segment on the line (regardless of type of arrowhead) represents one subgroup analysis. Analyses with strata for which the upper and lower boundaries are specified have a flat arrowhead while RCTs which split strata on an eGFR higher or lower than a certain threshold have pointed arrowheads. These arrows have conveniently been given a length of 15 ml/min/1.73m² but this length does not represent the upper or lower boundaries of the strata. The diamonds represent the mean eGFR reported in studies. This eGFR can lie outside the strata for which analyses have been performed (e.g. the REMINDER trial) or absent if no mean eGFR was reported (e.g. the ONTARGET trial). RCTs are represented once if they compare drugs within the same drug class (e.g. ace-inhibitors) or placebo and more than once if they compare drugs of different drug classed (e.g. ace-inhibitors vs angiotensin receptor blockers). RCTs which are more than once on the figure have the number in parentheses behind the name of the RCT. For example, the PEGUSUS- TIMI 54 trial, which compared acetylsalicylic acid + rivaroxaban with acetylsalicylic acid, performed a stratified analysis for participants with an eGFR >90, 60-90, 45-60, and <45 ml/min/1.73m² and the participants in this RCTs had a mean eGFR of 71 ml/min/1.73m².

eFigure 6: Heat map of (subgroup) analyses for all-cause mortality for people with different stages of CKD.



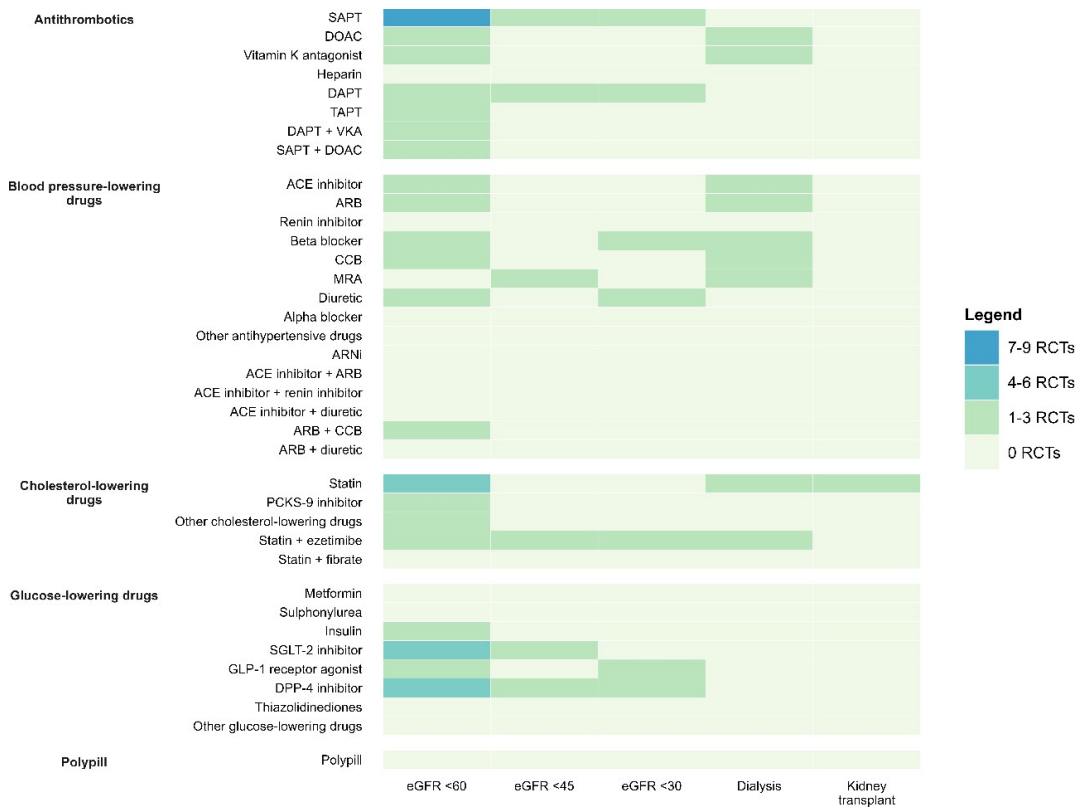
Abbreviations: ACE-inhibitor, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor-neprilysin inhibitor; CCB, calcium channel blocker; DAPT, double antiplatelet therapy; DOAC, direct oral anticoagulant; DPP-4 inhibitor, dipeptidyl-peptidase-4 inhibitors; eGFR, estimated glomerular filtration rate; GLP-1 receptor agonist, glucagon-like peptide-1 receptor agonist; MRA, mineralocorticoid receptor antagonist; PCSK-9 inhibitor, Proprotein convertase subtilisin/kexin type 9 inhibitor; SAPT, single antiplatelet therapy; SGLT-2 inhibitor, sodium-glucose cotransporter-2 inhibitor; TAPT, triple antiplatelet therapy; VKA, vitamin K antagonist.

eFigure 7: Heat map of (subgroup) analyses for cardiovascular mortality for people with different stages of CKD.



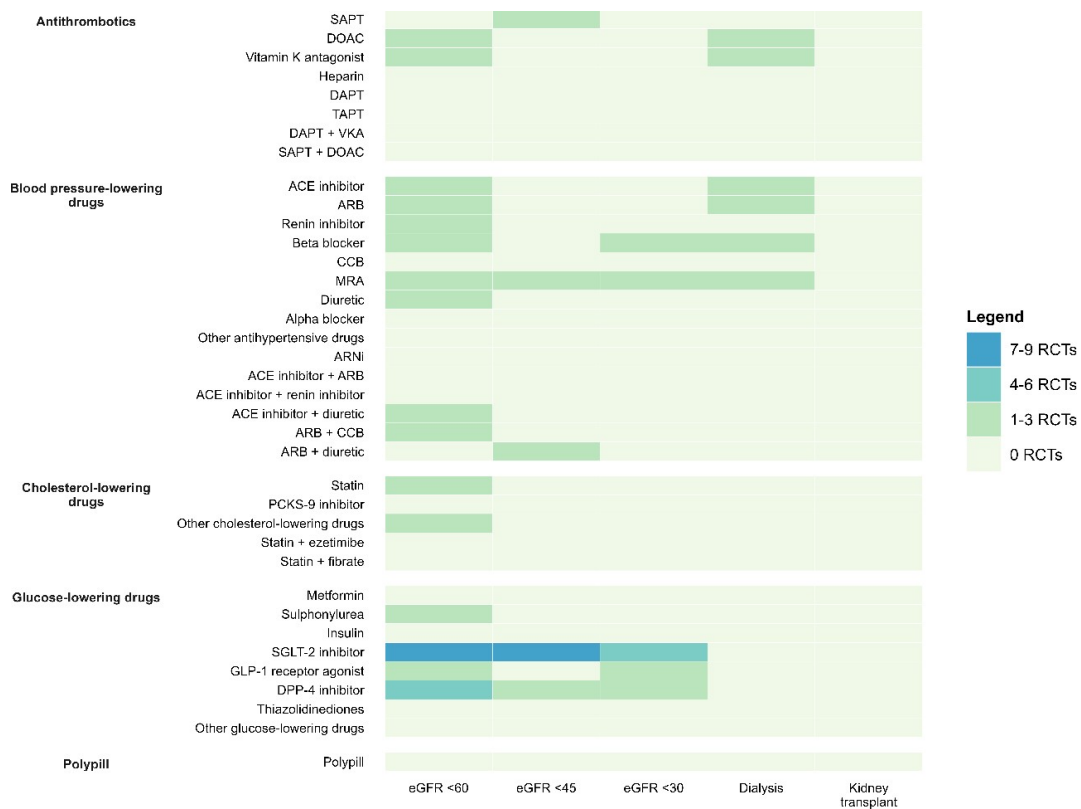
Abbreviations: ACE-inhibitor, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor-neprilysin inhibitor; CCB, calcium channel blocker; DAPT, double antiplatelet therapy; DOAC, direct oral anticoagulant; DPP-4 inhibitor, dipeptidyl-peptidase-4 inhibitors; eGFR, estimated glomerular filtration rate; GLP-1 receptor agonist, glucagon-like peptide-1 receptor agonist; MRA, mineralocorticoid receptor antagonist; PCSK-9 inhibitor, Proprotein convertase subtilisin/kexin type 9 inhibitor; SAPT, single antiplatelet therapy; SGLT-2 inhibitor, sodium-glucose cotransporter-2 inhibitor; TAPT, triple antiplatelet therapy; VKA, vitamin K antagonist.

eFigure 8: Heat map of (subgroup) analyses for coronary artery disease for people with different stages of CKD.



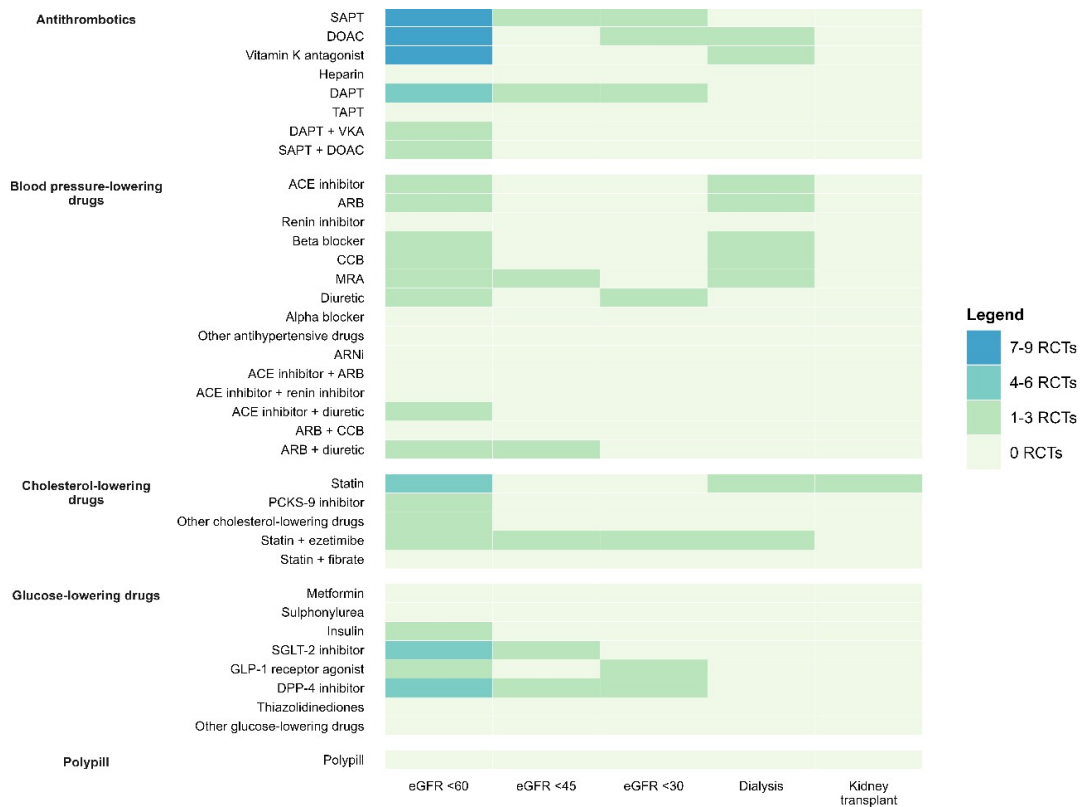
Abbreviations: ACE-inhibitor, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor-neprilysin inhibitor; CCB, calcium channel blocker; DAPT, double antiplatelet therapy; DOAC, direct oral anticoagulant; DPP-4 inhibitor, dipeptidyl-peptidase-4 inhibitors; eGFR, estimated glomerular filtration rate; GLP-1 receptor agonist, glucagon-like peptide-1 receptor agonist; MRA, mineralocorticoid receptor antagonist; PCSK-9 inhibitor, Proprotein convertase subtilisin/kexin type 9 inhibitor; SAPT, single antiplatelet therapy; SGLT-2 inhibitor, sodium-glucose cotransporter-2 inhibitor; TAPT, triple antiplatelet therapy; VKA, vitamin K antagonist.

eFigure 9: Heat map of (subgroup) analyses for heart failure for people with different stages of CKD.



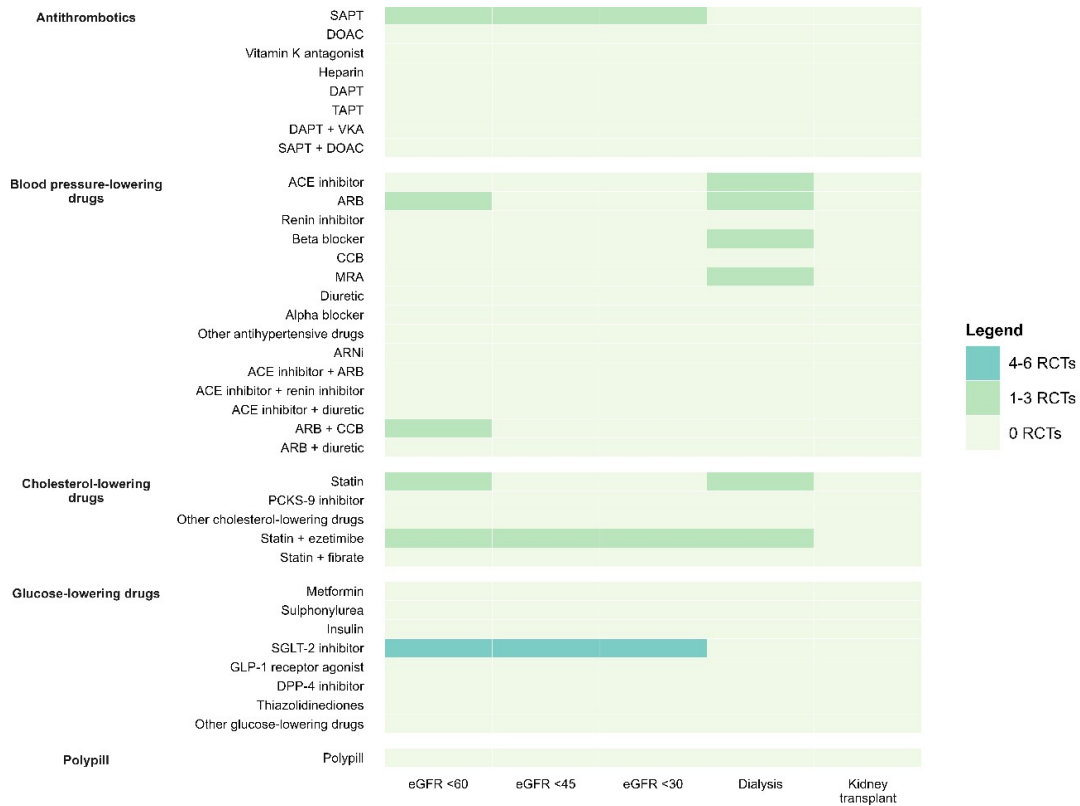
Abbreviations: ACE-inhibitor, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor-neprilysin inhibitor; CCB, calcium channel blocker; DAPT, double antiplatelet therapy; DOAC, direct oral anticoagulant; DPP-4 inhibitor, dipeptidyl-peptidase-4 inhibitors; eGFR, estimated glomerular filtration rate; GLP-1 receptor agonist, glucagon-like peptide-1 receptor agonist; MRA, mineralocorticoid receptor antagonist; PCSK-9 inhibitor, Proprotein convertase subtilisin/kexin type 9 inhibitor; SAPT, single antiplatelet therapy; SGLT-2 inhibitor, sodium-glucose cotransporter-2 inhibitor; TAPT, triple antiplatelet therapy; VKA, vitamin K antagonist.

eFigure 10: Heat map of (subgroup) analyses for cerebrovascular disease for people with different stages of CKD.



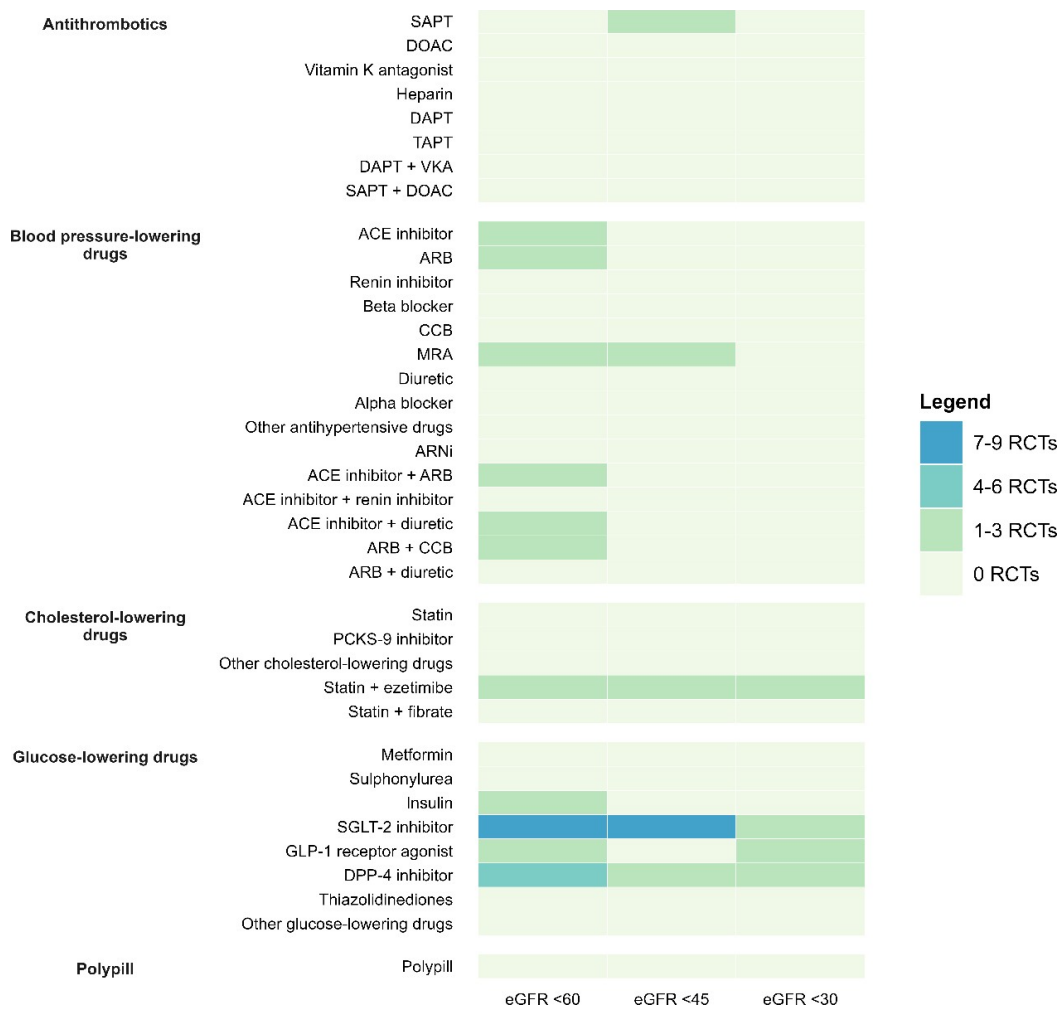
Abbreviations: ACE-inhibitor, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor-neprilysin inhibitor; CCB, calcium channel blocker; DAPT, double antiplatelet therapy; DOAC, direct oral anticoagulant; DPP-4 inhibitor, dipeptidyl-peptidase-4 inhibitors; eGFR, estimated glomerular filtration rate; GLP-1 receptor agonist, glucagon-like peptide-1 receptor agonist; MRA, mineralocorticoid receptor antagonist; PCSK-9 inhibitor, Proprotein convertase subtilisin/kexin type 9 inhibitor; SAPT, single antiplatelet therapy; SGLT-2 inhibitor, sodium-glucose cotransporter-2 inhibitor; TAPT, triple antiplatelet therapy; VKA, vitamin K antagonist.

eFigure 11: Heat map of (subgroup) analyses for peripheral arterial disease for people with different stages of CKD.



Abbreviations: ACE-inhibitor, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor-neprilysin inhibitor; CCB, calcium channel blocker; DAPT, double antiplatelet therapy; DOAC, direct oral anticoagulant; DPP-4 inhibitor, dipeptidyl-peptidase-4 inhibitors; eGFR, estimated glomerular filtration rate; GLP-1 receptor agonist, glucagon-like peptide-1 receptor agonist; MRA, mineralocorticoid receptor antagonist; PCKS-9 inhibitor, Proprotein convertase subtilisin/kexin type 9 inhibitor; SAPT, single antiplatelet therapy; SGLT-2 inhibitor, sodium-glucose cotransporter-2 inhibitor; TAPT, triple antiplatelet therapy; VKA, vitamin K antagonist.

eFigure 12: Heat map of (subgroup) analyses kidney failure for people with different stages of CKD.



Abbreviations: ACE-inhibitor, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor-neprilysin inhibitor; CCB, calcium channel blocker; DAPT, double antiplatelet therapy; DOAC, direct oral anticoagulant; DPP-4 inhibitor, dipeptidyl-peptidase-4 inhibitors; eGFR, estimated glomerular filtration rate; GLP-1 receptor agonist, glucagon-like peptide-1 receptor agonist; MRA, mineralocorticoid receptor antagonist; PCSK-9 inhibitor, Proprotein convertase subtilisin/kexin type 9 inhibitor; SAPT, single antiplatelet therapy; SGLT-2 inhibitor, sodium-glucose cotransporter-2 inhibitor; TAPT, triple antiplatelet therapy; VKA, vitamin K antagonist.