**Supplementary Tables**

for the Manuscript **“Serious Adverse Events in Patients with Target-Oriented Blood Pressure Management A Systematic Review”**

by Frey L et al.

Supplementary Table 1: Search strategy for Ovid MEDLINE®

|  |  |  |
| --- | --- | --- |
|  | **Searches** | **Results** |
| 1 | exp Hypertension/dt or ("blood pressure" adj3 (control\* or target\* or regulat\* or treat\* or lower\* or therap\*)).ti,ab. or (((goal\* or intensive\* or strict\* or  target\* or tight\*) adj5 (antihypertensive\* or "anti hypertensive\*or bp" or control or dbp or diastolic or pressure\* or sbp or systolic or treat\*)) and "blood  pressure").ti,ab. | 99647 |
| 2 | (((intensive or standard or strict or agressive or moderate or mild or higher or lower or moderate) adj1 (versus or vs or compar\*)) or ((intensive or strict or  agressive or thight) adj12 (standard or guideline\* or moderate or mild)) or (higher adj12 lower) or (("120" adj3 ("mm hg" or mmhg)) and ("130" adj3 ("mm  hg" or mmhg))) or (("120" adj3 ("mm hg" or mmhg)) and ("140" adj3 ("mm hg" or mmhg))) or (("130" adj3 ("mm hg" or mmhg)) and ("140" adj3 ("mm hg"  or mmhg))) or (optimal adj3 'blood pressure')).ti,ab. | 255003 |
| 3 | exp Antihypertensive Agents/ae or (adverse or side-effect\*).ti,ab,kf. | 625525 |
| 4 | ((randomised controlled trial or controlled clinical trial).pt. or clinical trials as topic/ or (random\* or crossover\* or cross-over\* or assign\* or allocat\* or  (doubl\* adj1 blind\*)).ti,ab. or trial.ti.) not (animals not humans).sh. | 1352568 |
| 5 | 1 and 2 and 3 and 4 | 333 |

Supplementary Table 2: SIGN checklist for randomized controlled trials

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Controlled Trials** | **1.1** | **1.2** | **1.3** | **1.4** | **1.5** | **1.6** | **1.7** | **1.8** | **1.9** | **1.10** | **2.1** |
|  | **I/C (%)** |
| **Original studies** | **SPRINT [6]** | Y | CS | CS | N | Y | Y | Y | 10.5 / 10.6 | Y | CS | ++ |
| **ACCORD [24]** | Y | Y | Y | N | Y | Y | Y | 4.3 / 3.8 | Y | CS | ++ |
| **Cardio-Sis [25]** | Y | Y | Y | N | Y | Y | Y | 13.3 / 12.7 | Y | CS | ++ |
| **AASK [35][23]** | Y | Y | N | N | Y | Y | Y | 29.6 / 32.5 | Y | CS | + |
| **VALISH [27]** | Y | CS | N | N | Y | Y | Y | 10.0 / 12.1 | Y | CS | + |
| **SPS3 [26]** | Y | Y | Y | N | Y | Y | Y | 11.9 / 12.0 | Y | CS | ++ |
| **JATOSpp [28]** | Y | CS | N | N | Y | Y | Y | 46.1 / 30.6 | N | CS | + |
| **Secondary studies** | **Margolis et al. [29]** | Y | Y | Y | N | Y | Y | Y | CS | CS | CS | + |
| **Cheung et al. [32]** | Y | CS | CS | N | Y | Y | Y | 10.2 / 12.3 | Y | CS | ++ |
| **Foy et al. [33]** | Y | CS | CS | N | N | Y | Y | CS | CS | CS | ++ |
| **Obi et al. [34]** | Y | CS | CS | N | Y | Y | Y | 10.8 / 11.1 | Y | CS | ++ |
| **Williamson et al. [36]** | Y | CS | CS | N | Y | Y | Y | 10.8 / 11.1 | Y | CS | ++ |
| **Beddhu et al. [30]** | Y | CS | CS | N | Y | Y | Y | 10.3 / 9.7 | Y | CS | ++ |
| **Bress et al. [31]** | Y | CS | CS | N | Y | Y | Y | F: 11.2 / 10.8 P: 8.9 / 10.0 | Y | CS | ++ |
| **Still et al. [35]** | Y | CS | CS | N | N | Y | Y | NHB: 11.8 / 11.4  NHW: 9.2 / 9.3 H: 12.7 / 14.6 | Y | CS | + |

SIGN Checklist [19]:

1.1, appropriate and clearly focused question; 1.2, assignment is randomized; 1.3, adequate concealment; 1.4, blinding; 1.5; treatment and control groups are similar at baseline; 1.6, The treatment under investigation is the only difference; 1.7, all relevant outcomes are measured; 1.8, percentage of drop-outs in each treatment arm; 1.9, intention to treat analysis; 1.10, various sites are comparable; 2.1, risk of bias: (++), high quality: most of the criteria have been fulfilled. If not fulfilled, the conclusions of the study are very unlikely to alter; (+), moderate quality: some criteria fulfilled. Criteria not adequately described are unlikely to alter the conclusions; (-), low quality: few or no criteria fulfilled. The conclusions are likely to alter.

Y = Yes; N = No; D = Does not apply; CS = Can't say; I = intervention; C = control; A = alternative

F= normal fasting glucose, P = prediabetes, NHB = Non-Hispanic Black, NHW = Non-Hispanic White, H = Hispanic

Supplementary Table 3: Studies characteristics

|  | **Design**  **(original study)** | **Characteristics of study participants** | **Baseline SBP/DBP (mmHg)** | **Target BP int vs. mod (mmHg)** | **Achieved BP int vs. mod (mmHg)** | **Difference BP int vs. mod (mmHg)** | **Definition of SAE** |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **SPRINT [6]** | multicenter RCT | Nondiabetic patients with SBP 130 mm Hg or higher, increased cardiovascular risk | 139.7/78.1 | SBP <120 vs. SBP <140 | 121.4 vs. 136.2 | 18.3 vs. 3.5 | fatal or life-threatening event with significant disability, prolonged hospitalization or judged by investigator as hazard to prevent mentioned events |
| **ACCORD [24]** | multicenter RCT | T2DM with age >40 y, cardiovascular disease or age >55 y with risk factors for cardiovascular disease | 139.2/76 | SBP <120 vs. SBP <140 | 119.3 vs. 133.5 | 19.9 vs. 5.7 | life threatening, resulted in permanent disability, hospitalization and considered by investigators as possibly related to antihypertensive medications |
| **Cardio-Sis [25]** | multicenter RCT | Nondiabetic patients with SBP ≥150 mm Hg, risk factor | 163.3/89.6 | SBP <130 vs. SBP <140 | 131.9 vs. 135.6 | 31.4 vs. 27.7 | NR |
| **AASK [23]** | multicenter RCT | HTN and eGFR 20-65 mL/min/1.73 m2, no other identified causes of renal insufficiency | 150/95.5 | MAP ≤92 vs. MAP 102-107 | 128.0 vs. 141.0 | 22 vs. 9 | NR |
| **VALISH [27]** | multicenter RCT | Age ≥70 and ≤85 y with SBP >160 mm Hg and DBP <90 mm Hg | 169.5/81.5 | SBP <140 vs. SBP ≥140 and <150 | 136.6 vs. 142.0 | 32.9 vs. 27.5 | NR |
| **SPS3 [26]** | multicenter RCT | Age ≥40 y with lacunar stroke | 143.0/78.5 | SBP <130 vs. SBP 130-149 | 127.0 vs. 138.0 | 16 vs. 5 | NR |
| **JATOSpp [28]** | Per Protocol Analysis RCT (JATOS) | HTN patients aged 65-85 y and SBP >160 mm Hg | 170.8/89.1 | SBP <140 vs. SBP <160 | 132.3 vs. 146.6 | 38.5 vs. 24.2 | NR |
| **Margolis et al. [29]** | secondary analysis RCT (ACCORD) | Participants of 54/77 ACCORD clinical centers | 138.3/75.4 | see ACCORD | 119.0 vs. 133.0 | 19.3 vs. 5.3 | see ACCORD |
| **Cheung et al. [32]** | secondary analysis RCT (SPRINT) | SPRINT participants with eGFR ≤60ml/min/1.73m2 | 139.1/75.0 | see SPRINT | 123.3 vs. 136.9 | 15.8 vs. 2.2 | see SPRINT |
| **Foy et al. [33]** | secondary analysis RCT (SPRINT) | SPRINT participants | 139.7/78.1 | see SPRINT | 120.4 vs. 135.8 | 19.3 vs. 3.9 | see SPRINT |
| **Obi et al. [34]** | secondary analysis RCT (SPRINT) | SPRINT participants | 139.7/78.1 | see SPRINT | 121.4 vs. 136.2 | 16.3 vs. 3.5 | see SPRINT |
| **Williamson et al. [36]** | secondary analysis RCT (SPRINT) | SPRINT participants with Age ≥75y | 141.6/71.2 | see SPRINT | 123.4 vs. 134.8 | 18.2 vs. 6.8 | see SPRINT |
| **Beddhu et al. [30]** | secondary analysis RCT (SPRINT) | SPRINT participants with eGFR ≥60ml/min/1.73m2 | 139.8/79.4 | see SPRINT | NR | NR | see SPRINT |
| **Bress et al. [31]** | secondary analysis RCT (SPRINT) | SPRINT participants | 139.7/78.1 | see SPRINT | 121.4 vs. 136.2 | 18.3 vs. 3.5 | see SPRINT |
| **Still et al. [35]** | secondary analysis RCT (SPRINT) | SPRINT participants with self-reported race/ethnicity | 139.6/78.1 | see SPRINT | 121.4 vs. 136.2 | 18.2 vs. 3.4 | see SPRINT |

BP = blood pressure, DBP = diastolic blood pressure, eGFR = estimated glomerular filtration rate, HTN = hypertension, int = intensive, MAP = mean arterial pressure,  
mod = moderate, NR = not reported, RCT = randomized control trial, SAE = serious adverse events, SBP = systolic blood pressure, T2DM = Type 2 diabetes mellitus, y = year(s)

Supplementary Table 4: Studies characteristics detailed

|  | **Inclusion criteria** | **Exclusion criteria** | **Primary outcome** | **Secondary outcome** |
| --- | --- | --- | --- | --- |
| **SPRINT [6]** | ≥50 years, SBP: 130 – 180 mm Hg on 0 or 1 medication SBP: 130 – 170 mm Hg on up to 2 medications SBP: 130 – 160 mm Hg on up to 3 medications SBP: 130 – 150 mm Hg on up to 4 medications, Risk (one or more): a) clinical or subclinical cardiovascular disease other than stroke b) CKD (eGFR 20 – 59 ml/min/1.73m2) and latest lab value, within the past 6 months. c) Framingham Risk Score for 10-year CVD risk ≥ 15% based on laboratory work done within the past 12 months for lipids d) Age ≥ 75 years. | Diabetes mellitus, stroke, not on disease-appropriate antihypertensives, secondary cause of hypertension, 1 min standing SBP <110 mmHg, proteinuria, polycystic kidney disease, Glomerulonephritis, eGFR < 20 mL/min/1.73 m2,cardiovascular event/procedure or hospitalization in prior 3 months, symptomatic heart failure in prior 6 months, LVEF <35%, life-limiting illness, poor adherence, organ transplant, unintentional weight loss >10% in prior 6 months, pregnancy, residence in a nursing home. | Composite of myocardial infarction, other acute coronary syndromes, stroke, heart failure, or death from cardiovascular causes | Individual components of the primary composite outcome, death from any cause, and the composite of the primary outcome or death from any cause |
| **ACCORD [24]** | Type 2 diabetes mellitus and HbA1c ≥ 7.5%, ≥40 years old with cardiovascular disease or 55 years of age or older with anatomical evidence of a substantial amount of atherosclerosis, albuminuria, left ventricular hypertrophy, or at least two additional risk factors for cardiovascular disease (dyslipidemia, hypertension, smoking, or obesity) | BMI ≥ 45, serum creatinine level ≥ 1.5 mg per deciliter (132.6 μmol/l), and other serious illness | First occurrence of a major cardiovascular event, which was defined as the composite of nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death. | Combination of the primary outcome plus revascularization or hospitalization for congestive heart failure; the combination of a fatal coronary event, nonfatal myocardial infarction, or unstable angina; nonfatal myocardial infarction; fatal or nonfatal stroke; nonfatal stroke; death from any cause; death from cardiovascular causes; and hospitalization or death due to heart failure. |
| **Cardio-Sis [25]** | ≥ 55 years old with a systolic blood pressure ≥150 mm Hg, with antihypertensive treatment for at least 12 weeks, had to have at least one additional risk factor, as described in the guidelines of the European Society of Hypertension (cigarette smoking, total cholesterol ≥5.2 mmol/L, HDL cholesterol <1.0 mmol/L, LDL cholesterol ≥3.4 mmol/L, family history of premature cardiovascular disease in first degree relative [<65 years in women and <55 years in men], previous transient ischaemic attack or stroke, or established coronary or peripheral arterial disease) | Fasting glucose of ≥7·0 mmol/L and those with a history of diabetes, any disease reducing life expectancy, renal dysfunction (serum creatinine >176.8 μmol/L), clinically relevant hepatic or haematological disorders, valvular heart disease, disorders confusing the electrocardiographic diagnosis of left ventricular hypertrophy (complete right or left bundle block, Wolff -Parkinson-White syndrome, previous Q-wave myocardial infarction, and paced heart rhythm), atrial fibrillation, and substance misuse. | Electrocardiographic left ventricular hypertrophy at the final 2-year visit | Composite of all-cause mortality, fatal or non-fatal myocardial infarction, fatal or non-fatal stroke, transient ischaemic attack, congestive heart failure of New York Heart Association stages III or IV requiring admission to hospital, angina pectoris with objective evidence of myocardial ischaemia, new-onset atrial fibrillation, coronary revascularisation, aortic dissection, occlusive peripheral arterial disease, and renal failure requiring dialysis. The single components of the main secondary outcome and the baseline-adjusted difference between groups in the achieved systolic blood pressure. |
| **AASK [23]** | African Americans with hypertension, aged 18 to 70 years with a eGFR between 20 and 65 mL/min per 1.73 m2 and no other identified causes of renal insufficiency | DBP of less than 95 mm Hg, known history of diabetes mellitus (fasting glucose ≥140 mg/dL or random glucose ≥200 mg/ dL), urinary protein to creatinine ratio of more than 2.5, accelerated or malignant hypertension within 6 months, secondary hypertension, evidence of non–BP-related causes of chronic kidney disease, serious systemic disease, clinical congestive heart failure, or specific indication for or contraindication to a study drug or study procedure | Rate of change in eGFR | Reduction in eGFR by 50% or by 25 mL/min per 1.73 m2 from the mean of the 2 baseline eGFRs; ESRD (dialysis or transplantation); or death. Urinary protein excretion, expressed as the urinary protein to creatinine ratio from a 24-hour urine collection. All cardiovascular events including cardiovascular deaths and hospitalizations for myocardial infarctions, strokes, heart failure, revascularization procedures, and other hospitalized cardiovascular events |
| **VALISH [27]** | Systolic hypertension on 1 or no BP-lowering medication, aged ≥70 years and had uncontrolled hypertension | Additional vascular risk factors to hypertension, diabetes mellitus, recurrent falls, contraindication to >1 antihypertensive medications, previous stroke, myocardial infarction, angina, peripheral vascular disease, cognitive impairment (mini-mental examination, MMSE <27), contraindication to MRI | Composite of cardiovascular events: sudden death, fatal or nonfatal stroke, fatal or nonfatal myocardial infarction, death because of heart failure, other cardiovascular death, unplanned hospitalization for cardiovascular disease, and renal dysfunction (doubling of serum creatinine to a level ≥2.0 mg per 100 mL or introduction of dialysis) | Each components of the primary end point, total mortality, and new onset or exacerbation of angina pectoris. Cardiovascular death, fatal or nonfatal myocardial infarction, and fatal or nonfatal stroke excluding transient ischemic attacks. |
| **SPS3 [26]** | Lacunar stroke clinical syndromes lasting >24h: Pure motor haemiparesis (PMH), Pure sensory stroke, Sensorimotor stroke, Ataxic hemiparesis, Dysarthria-clumsy hand syndrome, Hemiballism, PMH with facial sparing, PMH with horizontal gaze palsy, PMH with contralateral III palsy, PMH with contralateral VI palsy, Cerebellar ataxia with contralateral III palsy, Pure dysarthria or Subcortical TIA with positive DWI on MRI | Disabling stroke (modified Rankin scale<4), previous intracranial haemorrhage (excluding traumatic) or haemorrhagic stroke, age under 30 years, high risk of bleeding, requirement for long-term use of anticoagulants or other antiplatelets, prior cortical or retinal stroke/TIA, prior ipsilateral carotid endarterectomy/stent, impaired renal function: glomerular filtration rate≤ 40ml/min, contraindications to aspirin or clopidogrel, Folstein Mini Mental Status Examination score< 24, contraindication to MRI, pregnancy or women of child-bearing potential who are not following an effective method of contraception, unlikely to be compliant with therapy/unwilling to return for frequent clinic visits, Patients concurrently participating in another study , other likely specific cause of stroke | Reduction in all stroke (including ischaemic strokes and intracranial haemorrhages) | Reductions in acute myocardial infarction, need for acute admission to hospital for a major vascular event, and death (vascular, non-vascular or unknown) |
| **JATOSpp [28]** | Outpatients, 65 to 85 years of age, essential hypertension (SBP ≥160 mmHg during the run-in period). Untreated or had received the same drug(s) for at least 4 weeks. Treated subjects were eligible if efonidipine could be added or substituted for one of the drugs given before study entry | Receiving efonidipine, a DBP of 120 mmHg or above, secondary hypertension, recent stroke (≤6 months previously) or signs and symptoms of stroke, a recent myocardial infarction or coronary angioplasty (≤6 months previously), angina pectoris requiring hospitalization, congestive heart failure of NYHA class II or higher, persistent arrhythmias, dissecting aneurysm of the aorta or occlusive arterial disease, hypertensive retinopathy, ALAT/ASAT ≥ 2x ULN, poorly controlled diabetes mellitus (fasting blood sugar of 200 mg/dl or higher or HbA1c of 8% or higher), renal dysfunction (serum creatinine of 1.5 mg/dl or higher), or malignant disease or collagen disease. Patients considered unsuitable as subjects were excluded. | Cerebrovascular disease (cerebral hemorrhage, cerebral infarction, transient ischemic attack, subarachnoid hemorrhage, and other types of cerebrovascular disease), cardiac disease (myocardial infarction, angina pectoris requiring hospitalization, and heart failure), vascular disease (dissecting aneurysms of the aorta and occlusive arterial disease), and renal dysfunction (acute or chronic renal failure; creatinine to a value of 1.5 mg/dl or higher). | Deaths from any cause, morbidity other than cardiovascular disease, changes in BP and heart rate, and any problems in regard to safety |
| **Margolis et al. [29]** | Reported fracture events in ACCORD | see ACCORD + Pathological fractures (secondary to neoplasm, necrosis, or sepsis, or periprosthetic fractures) | Non-spine fractures | Hip, proximal humerus, distal forearm, ankle and foot fractures |
| **Cheung et al. [32]** | SPRINT participants with CKD | NR | see SPRINT | Main kidney outcome: defined as the composite of 50% decrease in eGFR from baseline or ESRD |
| **Foy et al. [33]** | see SPRINT | see SPRINT | see SPRINT, association with gender | NR |
| **Obi et al. [34]** | see SPRINT | see SPRINT + missing eGFR | see SPRINT | see SPRINT + renal outcome: acute kidney injury, with/without CKD ≥50%/≥30% decrease in eGFR, end-stage renal disease. Incident albuminuria |
| **Williamson et al. [36]** | SPRINT participants with age ≥75 years | see SPRINT | see SPRINT | see SPRINT |
| **Beddhu et al. [30]** | SPRINT participants with eGFR ≥60ml/min/1.73m2 | see SPRINT | see SPRINT | see SPRINT + renal outcome: acute kidney injury, with/without CKD ≥50%/≥30% decrease in eGFR, end-stage renal disease. Incident albuminuria |
| **Bress et al. [31]** | see SPRINT | see SPRINT | see SPRINT, association with prediabetes and normoglycemia | see SPRINT + renal outcome: acute kidney injury, with/without CKD ≥50%/≥30% decrease in eGFR, end-stage renal disease. Incident albuminuria |
| **Still et al. [35]** | see SPRINT | other race/ethnicity categories than non-hispanic black, non-hispanic white, hispanic | see SPRINT | see SPRINT + renal outcome: acute kidney injury, with/without CKD ≥50%/≥30% decrease in eGFR, end-stage renal disease. Incident albuminuria |

ALAT alanine transaminase, ASAT aspartate transaminase, BMI body mass index, BP blood pressure, CKD chronic kidney disease, CVD cardiovascular disease, DBP diastolic blood pressure, eGFR estimated glomerular filtration rate, ESRD end-stage renal disease, HDL high density lipoprotein, LDL low density lipoprotein, LVEF left ventricular ejection fraction, MMSE Mini-Mental State Examination, MRI magnetic resonance imaging, NR not reported, NYHA New York Heart Association, SBP systolic blood pressure, TIA transient ischemic attack,

Supplementary Table 5: Frequencies of additional adverse events in original studies (in %)

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | **Swelling/ Hives** | **Lighthead.** | **Bradyc. / Arrhyt.** | **Electrolyte Abnorm.** | **Stroke** | **Blurred vision** | **Unstead.** | **Diarrhoea** | **Dyspnea** | **Edema** | **Asthenia** |
| **ACCORD [24]** | int. | 8.8 | - | 0.5 | - | - | - | - | - | - | - | - |
| **(n=4733)** | mod. | 8.8 | - | 0.1 | - | - | - | - | - | - | - | - |
|  |  |  |  |  |  |  |  |  |  |  |  |  |
| **Cardio-Sis [25]** | int. | 5.9 | - | - | - | - | - | - | 1.3 | - | - | 2.3 |
| **(n=1111)** | mod. | 6.3 | - | - | - | - | - | - | 0.9 | - | - | 0.9 |
|  |  |  |  |  |  |  |  |  |  |  |  |  |
| **SPS3 [26]** | int. | - | 14.8 | - | - | 0.1 | 5.7 | 25.0 | - | - | - | - |
| **(n=3020)** | mod. | - | 15.5 | - | - | 0.1 | 6.8 | 23.4 | - | - | - | - |
|  |  |  |  |  |  |  |  |  |  |  |  |  |
| **AASK [23]** | int. | - | 51.2 | - | - | - | - | - | - | 48.4 | 55.1 | - |
| **(n=1094)** | mod. | - | 49.2 | - | - | - | - | - | - | 45.8 | 54.2 | - |
|  |  |  |  |  |  |  |  |  |  |  |  |  |
| **JATOSpp [28]** | int. | - | 0.3 | - | - | - | - | - | - | - | - | - |
| **(n=2722)** | mod. | - | 0.3 | - | - | - | - | - | - | - | - | - |
|  |  |  |  |  |  |  |  |  |  |  |  |  |
| **SPRINT [6] \*** | int. | - | - | - | 2.0 | - | - | - | - | - | - | - |
| **(n=9361)** | mod. | - | - | - | 1.3 | - | - | - | - | - | - | - |
|  |  |  |  |  |  |  |  |  |  |  |  |  |
| **SPRINT [6]** ¤ | int. | - | - | - | 3.8 | - | - | - | - | - | - | - |
| **(n=9361)** | mod. | - | - | - | 2.8 | - | - | - | - | - | - | - |

Int. = intensive, mod. = moderate, y = year(s), AKI = acute kidney injury, Lighthead. = Lightheadedness, Bradyc. = Bradycardia, Arrhyt. = Arrhythmia, Abnorm. = Abnormalties, Unstead. = Unsteadiness

- = not reported , \* = all serious adverse events, ¤ = treatment related serious adverse events

Supplementary Table 6: Frequencies of serious adverse events in secondary studies (in %)

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Study Participants Characteristics** | **Hypotension** | | **Syncope** | | **Injurious falls** | | **Bradycardia** | | **Electrolyte abnorm.** | | **AKI** | | **Fractures** | |
|  |
|  |  | int. | mod. | int. | mod. | int. | mod. | int. | mod. | int. | mod. | int. | mod. | int. | mod. |
| **Bress et al. [31]** | Prediabetes | 3.4 | 1.7 | 3.5 | 2.3 | 6.6 | 6.4 | 2.3 | 1.8 | 3.9 | 3 | 4.5 | 2.5 | - | - |
| **Bress et al. [31]** | Normoglykemia | 3.3 | 2.2 | 3.4 | 2.5 | 7.3 | 7.7 | 2.1 | 1.8 | 3.6 | 2.6 | 4.1 | 2.6 | - | - |
| **Cheung et al. [32]** | CKD | 3.8 | 2.9 | 4.1 | 3.2 | 9.4 | 10.5 | 2.8 | 3 | 5.2 | 3.9 | 8.6 | 5.9 | - | - |
| **Foy et al. [33]** | Women | 2.4 | 1.5 | 3.4 | 2.2 | 9.8 | 8.2 | 1.7 | 1.6 | 5.6 | 3.7 | 3.3 | 1.9 | - | - |
| **Foy et al. [33]** | Men | 3.4 | 1.8 | 3 | 2.1 | 5.7 | 6 | 2.2 | 1.6 | 2.5 | 2.2 | 4.8 | 2.9 | - | - |
| **Obi et al. [34]** | GFR<45ml/min | - | - | - | - | - | - | - | - | - | - | 13.9 | 8.5 | - | - |
| **Obi et al. [34]** | GFR 45-60ml/min | - | - | - | - | - | - | - | - | - | - | 5.9 | 4.7 | - | - |
| **Obi et al. [34]** | GFR 60-90ml/min | - | - | - | - | - | - | - | - | - | - | 2.4 | 1.2 | - | - |
| **Obi et al. [34]** | GFR >90ml/min | - | - | - | - | - | - | - | - | - | - | 2.4 | 1 | - | - |
| **Still et al. [35]** | Non-Hispanic White | 1.4 | 1 | 1.4 | 1.1 | 3.4 | 4.3 | 1.2 | 1.1 | 1.8 | 1.4 | 2.4 | 1.8 | - | - |
| **Still et al. [35]** | Non-Hispanic Black | 0.8 | 0.8 | 0.7 | 0.5 | 1.9 | 1.5 | 0.3 | 0.6 | 1.2 | 0.9 | 3.1 | 1.6 | - | - |
| **Still et al. [35]** | Hispanic | 0.4 | 0 | 1 | 0.6 | 1.2 | 0.4 | 0.2 | 0.6 | 0.8 | 0 | 1.2 | 1 | - | - |
| **Williamson et al. [36]** | Age≥75y | 3.3 | 2 | 4.3 | 3.3 | 11.6 | 14.1 | 3.6 | 3.3 | 4.6 | 3.3 | 5.5 | 4.2 | - | - |
| **Margolis et al. [29]** | Follow-up fractures | - | - | - | - | - | - | - | - | - | - | - | - | 7.6 | 9.8 |

Int. = intensive, mod. = moderate, y = year(s), AKI = acute kidney injury, Abnorm. = Abnormalties, GFR = Glomerular filtration rate, CKD = chronic kidney disease, SAE = serious adverse events

- = not reported ,