***Online-only Supplementary Material***

**MASLD: a systemic metabolic disorder with cardiovascular and malignant complications**

**Supplementary Table 1.** Drugs that potentially reduce CVD risk and that are beneficial (or harmless) for MASLD.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Drug  classes | Drugs | Principal site and mode of action | Indications for use | Benefit on CVD risk factors | Benefit on CVD endpoints and all-cause mortality | Adverse  effects |
| *Sodium-glucose cotransporter 2 inhibitors (SGLT2is) [1, 2, 3]* | Gliflozins,  e.g., dapagliflozin, canagliflozin, empaglifozin | SGLT2 is almost exclusively in the luminal membrane of epithelial cells lining the first and second segments of the proximal tubules, where it mediates reabsorption of most (≥90%) filtered glucose. Inhibition of the SGLT2 cotransporter in the proximal convoluted tubule in the kidney, causing loss of glucose reabsorption in the kidney  Inhibition of SGLT2 results in a greater sodium concentration in the renal proximal tubule, resulting in more sodium passing along the nephron. Sodium is sensed by the macula cells, which act via adenosine to constrict afferent glomerular arterioles | Type 2 diabetes and hyperglycemia  Heart failure with reduced left ventricular ejection fraction and emerging evidence of benefit with mid-range ejection fraction and preserved ejection fraction  Randomized controlled trial evidence not convincing for benefit in MASH | The nephroprotective effects are class effects observed in people with normal or impaired eGFR values  Protect the glomeruli by reducing the intraglomeruli pressure  HbA1c reduction ~10 mmol/mol  Reduced eGFR decline  Decrease in abnormal albuminuria  Weight loss ~3-6 kg | Major nonfatal CVD events ~15% decrease  CVD death ~20% decrease  Nonfatal myocardial infarction ~15% decrease  Heart failure hospitalization ~35% decrease  All-cause mortality ~17% decrease [1] | Initial decrease in eGFR that recovers on treatment over time (randomized trials show a slower decline over time than placebo)  Most drugs are not recommended when eGFR <45 mL/ml/1.73 m2  Contrary to initial concerns, the risks of urinary tract infection and acute kidney injury are less common than expected |
| *Incretin receptor agonists: glucagon like peptide-1 (GLP-1) receptor agonists [2, 3, 4, 5] and glucose-dependent insulinotropic polypeptide (GIP) agonists[6]* | GLP-1 receptor agonists,  e.g., subcutaneous semaglutide, liraglutide  Dual GIP receptor agonists & GLP-1 receptor agonists,  e.g., tirzepatide | Incretin receptor agonists act centrally on appetite regulation to decrease dietary energy intake | Type 2 diabetes and obesity  Randomized controlled trial evidence of benefit in MASH | Weight loss of 10-15% is achievable  Improvement in blood pressure, abdominal obesity, and atherogenic lipoprotein phenotype (see text for description)  A decrease in HbA1c depends on the amount of weight loss and residual pancreatic beta cell function. | Major adverse cardiovascular events  CVD death and  all-cause mortality  GLP-1 receptor agonists: recent meta-analyses show there are significant reductions in major CVD events (~12%), composite CVD death/heart failure (HF) hospitalization (~24%), and composite renal outcome (~18%)\* [4]  Tirzepatide: a recent meta-analysis of participants treated with tirzepatide versus control participants showed a ~20% nonsignificant benefit in major CVD events, a nonsignificant ~10% reduction in CVD death and a ~20% nonsignificant decrease in all-cause mortality[6] | Nausea, vomiting, indigestion |
| *Angiotensin II receptor blockers (AT-II), Renin-angiotensin system (RAS) inhibitors or mineralocorticoid receptor antagonists (MRAs) [7]* | a) AT-II receptor inhibitors (sartans); angiotensin  b) RAS inhibitors (ACE-I);  c) MRAs  e.g., a) losartan, candesartan; b)  ramipril, perindopril; and c) finerenone | ACE inhibitors inhibit the activity of angiotensin-converting enzyme, an important enzyme within the renin-angiotensin system that converts angiotensin 1 to angiotensin II and hydrolyses bradykinin. Therefore, ACE-I decrease the formation of angiotensin (a vasoconstrictor) and increase bradykinin (a vasodilator)  Finerenone is a non-steroidal mineralocorticoid receptor antagonist that inhibits receptor-mediated sodium reabsorption and decreases receptor overactivation, thereby reducing the inflammation and fibrosis that lead to kidney damage | ACE inhibitors and AT-II receptor inhibitors are a class of medications used for the treatment of hypertension, heart failure, diabetic nephropathy, and in patients with post-myocardial infarction to decrease the CVD risk of a recurrent vascular event  Finerenone is indicated for CKD stage ≥3 with albuminuria associated with type 2 diabetes (if serum-potassium ≤5 mmol/L and eGFR ≥60 mL/min/1.73 m2)  Randomized controlled trial evidence lacking for evidence of benefit in MASH | Blood pressure reduction to <130 mmHg (systolic) and  70-80 mmHg (diastolic) | Among patients with increased CVD risk, reduction of systolic blood pressure to <130 mmHg has been shown to reduce CVD events by 25% and all-cause death by 27%  Optimal diastolic blood pressure for clinical outcomes appears to be in the range of 70 to 80 mmHg [8, 9, 10, 11] | Well tolerated, but cough is a common side effect with ACE inhibitors.  Finerenone is contraindicated in Addison’s disease or with hyperkalemia  Common side effects: hyperkalemia, hypotension and pruritus |
| *Peroxisome proliferator-activated receptor (PPAR)-gamma agonist- pioglitazone [2, 3, 12] and*  *including the pan-PPAR agonist lanifibranor\* [13]* | PPAR-gamma agonists,  i.e., pioglitazone  Pan-PPAR agonists,  i.e., lanifibranor\* | Agonists of the nuclear hormone receptor PPAR-gamma. PPAR-gamma 2 is predominantly expressed in adipose tissue and the immune system, and it also induces the differentiation of adipocytes, myogenic cells, and mononuclear phagocytes  Also expressed in vascular endothelial cells, hepatic stellate and Kupffer cells, in the kidney and the urinary system in the medullary collecting duct, paraurethral and bladder epithelial cells, podocytes, and mesangial cells [14] | Treatment of type 2 diabetes  Randomized controlled trial evidence shows benefit in MASH with pioglitazone and in a phase 2b trial with lanifibranor | Decrease in ectopic fat accumulation.  Increase in insulin sensitivity, improves insulin signaling and facilitates glucose via increasing GLUT-4 expression  Decreases plasma glucose and Increases serum adiponectin. Polarizes macrophages to the anti-inflammatory M2 type | In a meta-analysis, pioglitazone was associated with a significantly lower risk of major cardiovascular events (~40%) and a higher risk of hospitalization for heart failure (~30%) | Pioglitazone contraindicated with left ventricular dysfunction/heart failure; previous non-traumatic bone fracture, or previous bladder cancer  Pioglitazone common side effects: moderate weight gain (increase in body fat and fluid retention) |
| *Lipid-lowering agents: statins [15, 16, 17, 18, 19]*  *ezetimibe [20]* | Statins  e.g., simvastatin, atorvastatin, rosuvastatin | Statins inhibiting HMG-CoA reductase in the liver and increase hepatic expression of LDL-receptors to lower plasma LDL-C concentration  Ezetimibe inhibits the Niemann-Pick C1-like 1 (NPC1L1) transmembrane protein. NPC1L1 is located at the apical membrane of enterocytes and the canalicular membrane of hepatocytes. It functions as a sterol transporter to mediate intestinal cholesterol absorption and counterbalances hepatobiliary cholesterol excretion | LDL-C lowering agents for decreasing CVD risk.  Randomized controlled trial evidence lacking for evidence of benefit in MASH | Statins significantly reduce plasma LDL-C levels (the effect is dose-related  High-dose statins (e.g., atorvastatin 80 mg/day) significantly reduce plasma triglycerides  Statins also significantly reduce plasma C-reactive protein concentrations | Statins significantly decrease the risk of acute myocardial infarction by ~35%, stroke by ~20%, CVD death by ~25% and all-cause death by ~15%  In adults at high CVD risk but without prior CVD events, statins are associated with reduced risk of CVD events and all-cause mortality  Benefits of statin therapy appear to be maintained across diverse demographic and clinical populations, with consistent benefits in groups defined by clinical characteristics.  (N.B. consensus is that statins are safe in MASLD)  Ezetimibe with statins reduces the risk of major CVD events by ~6% compared to statins alone. Probable benefit of ezetimibe alone | All statins are associated with an increased risk of serum transaminase elevation. All statins are associated with an increased risk of muscle problems (rosuvastatin >atorvastatin >simvastatin) |
| *Thyroid hormone receptor-beta agonists [21]*  *(MAESTRO clinical program\*\*)* | Resmetirom | Acts as thyroid hormone receptor-beta agonist in the liver | Phase 3 randomized control trial shows benefit in MASLD (i.e., MAESTRO-NAFLD-1) and other phase 3 MAESTRO trials are ongoing for treatment of MASH and liver fibrosis | Resmetirom leads to significant reductions in plasma LDL-cholesterol (~15%) and triglycerides (~20%) and lipoprotein (a) (~20%) | No CVD endpoint data to date | Higher incidence of  transient mild diarrhea and nausea with resmetirom than placebo  No significant effects on plasma thyroid  stimulating hormone, free triiodothyronine and free thyroxine concentrations, bone mineral  density, heart rate, or cardiovascular markers |

N.B.: There may be ethnic differences in the effects of GLP-1 receptor agonists on clinical outcomes. \*These effects were not observed in black ethnicity groups, although the numbers in the trials were small. \*\*All participants included in the phase 3 MAESTRO resmetirom clinical program had at least three metabolic risk factors and were ≥18 years of age.

**References**

1 Bailey CJ, Day C, Bellary S. Renal Protection with SGLT2 Inhibitors: Effects in Acute and Chronic Kidney Disease. Current diabetes reports 2022;**22**:39-52.

2 Mannucci E, Gallo M, Giaccari A, Candido R, Pintaudi B, Targher G*, et al.* Effects of glucose-lowering agents on cardiovascular and renal outcomes in subjects with type 2 diabetes: An updated meta-analysis of randomized controlled trials with external adjudication of events. Diabetes Obes Metab 2023;**25**:444-53.

3 de Carvalho LSF, Nogueira ACC, Bonilha I, Luchiari B, Benchimol A, Couri CEB*, et al.* Glucose-Lowering and the Risk of Cardiovascular Events With Antidiabetic Therapies: A Systematic Review and Additive-Effects Network Meta-Analysis. Frontiers in cardiovascular medicine 2022;**9**:876795.

4 Kunutsor SK, Khunti K, Seidu S. Racial, ethnic and regional differences in the effect of sodium-glucose co-transporter 2 inhibitors and glucagon-like peptide 1 receptor agonists on cardiovascular and renal outcomes: a systematic review and meta-analysis of cardiovascular outcome trials. Journal of the Royal Society of Medicine 2023:1410768231198442.

5 Lincoff AM, Brown-Frandsen K, Colhoun HM, Deanfield J, Emerson SS, Esbjerg S*, et al.* Semaglutide and Cardiovascular Outcomes in Obesity without Diabetes. New England Journal of Medicine 2023.

6 Sattar N, McGuire DK, Pavo I, Weerakkody GJ, Nishiyama H, Wiese RJ*, et al.* Tirzepatide cardiovascular event risk assessment: a pre-specified meta-analysis. Nature medicine 2022;**28**:591-8.

7 Morales J, Handelsman Y. Cardiovascular Outcomes in Patients With Diabetes and Kidney Disease: JACC Review Topic of the Week. J Am Coll Cardiol 2023;**82**:161-70.

8 Sobieraj P, Lewandowski J, Siński M, Gaciong Z. Determination of optimal on-treatment diastolic blood pressure range using automated measurements in subjects with cardiovascular disease-Analysis of a SPRINT trial subpopulation. Journal of clinical hypertension (Greenwich, Conn) 2019;**21**:911-8.

9 Wright JT, Jr., Williamson JD, Whelton PK, Snyder JK, Sink KM, Rocco MV*, et al.* A Randomized Trial of Intensive versus Standard Blood-Pressure Control. N Engl J Med 2015;**373**:2103-16.

10 D'Anci KE, Tipton K, Hedden-Gross A, Rouse B, Hermanson L, Fontanarosa J. Effect of Intensive Blood Pressure Lowering on Cardiovascular Outcomes: A Systematic Review Prepared for the 2020 U.S. Department of Veterans Affairs/U.S. Department of Defense Guidelines. Ann Intern Med 2020;**173**:895-903.

11 Bundy JD, Li C, Stuchlik P, Bu X, Kelly TN, Mills KT*, et al.* Systolic Blood Pressure Reduction and Risk of Cardiovascular Disease and Mortality: A Systematic Review and Network Meta-analysis. JAMA Cardiol 2017;**2**:775-81.

12 Zhou Y, Huang Y, Ji X, Wang X, Shen L, Wang Y. Pioglitazone for the Primary and Secondary Prevention of Cardiovascular and Renal Outcomes in Patients with or at High Risk of Type 2 Diabetes Mellitus: A Meta-Analysis. J Clin Endocrinol Metab 2020;**105**.

13 Francque S, Szabo G, Abdelmalek MF, Byrne CD, Cusi K, Dufour JF*, et al.* Nonalcoholic steatohepatitis: the role of peroxisome proliferator-activated receptors. Nat Rev Gastroenterol Hepatol 2021;**18**:24-39.

14 Qiu Y, Gan M, Wang X, Liao T, Chen Q, Lei Y*, et al.* The global perspective on peroxisome proliferator-activated receptor γ (PPARγ) in ectopic fat deposition: A review. International journal of biological macromolecules 2023;**253**:127042.

15 Wang X, Li J, Wang T, Zhang Z, Li Q, Ma D*, et al.* Associations between statins and adverse events in secondary prevention of cardiovascular disease: Pairwise, network, and dose-response meta-analyses of 47 randomized controlled trials. Frontiers in cardiovascular medicine 2022;**9**:929020.

16 Cai T, Abel L, Langford O, Monaghan G, Aronson JK, Stevens RJ*, et al.* Associations between statins and adverse events in primary prevention of cardiovascular disease: systematic review with pairwise, network, and dose-response meta-analyses. Bmj 2021;**374**:n1537.

17 He WB, Ko HTK, Curtis AJ, Zoungas S, Woods RL, Tonkin A*, et al.* The Effects of Statins on Cardiovascular and Inflammatory Biomarkers in Primary Prevention: A Systematic Review and Meta-Analysis. Heart, lung & circulation 2023;**32**:938-48.

18 Yang XH, Zhang BL, Cheng Y, Fu SK, Jin HM. Statin use and the risk of CVD events, stroke, and all-cause mortality in patients with diabetes: A systematic review and meta-analysis. Nutr Metab Cardiovasc Dis 2022;**32**:2470-82.

19 Chou R, Cantor A, Dana T, Wagner J, Ahmed AY, Fu R*, et al.* Statin Use for the Primary Prevention of Cardiovascular Disease in Adults: Updated Evidence Report and Systematic Review for the US Preventive Services Task Force. Jama 2022;**328**:754-71.

20 Zhan S, Tang M, Liu F, Xia P, Shu M, Wu X. Ezetimibe for the prevention of cardiovascular disease and all-cause mortality events. The Cochrane database of systematic reviews 2018;**11**:Cd012502.

21 Harrison SA, Taub R, Neff GW, Lucas KJ, Labriola D, Moussa SE*, et al.* Resmetirom for nonalcoholic fatty liver disease: a randomized, double-blind, placebo-controlled phase 3 trial. Nature medicine 2023.