***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.

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| 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 hyperglycemiaHeart 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 valuesProtect the glomeruli by reducing the intraglomeruli pressureHbA1c reduction ~10 mmol/molReduced eGFR decline Decrease in abnormal albuminuriaWeight loss ~3-6 kg | Major nonfatal CVD events ~15% decrease CVD death ~20% decreaseNonfatal myocardial infarction ~15% decreaseHeart failure hospitalization ~35% decreaseAll-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 m2Contrary 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, liraglutideDual 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 obesityRandomized 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 eventsCVD death andall-cause mortalityGLP-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) MRAse.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 eventFinerenone 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 hyperkalemiaCommon 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 phagocytesAlso 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 diabetesRandomized 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 expressionDecreases 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]* | Statinse.g., simvastatin, atorvastatin, rosuvastatin | Statins inhibiting HMG-CoA reductase in the liver and increase hepatic expression of LDL-receptors to lower plasma LDL-C concentrationEzetimibe 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-relatedHigh-dose statins (e.g., atorvastatin 80 mg/day) significantly reduce plasma triglyceridesStatins 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 mortalityBenefits 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 oftransient mild diarrhea and nausea with resmetirom than placeboNo significant effects on plasma thyroidstimulating hormone, free triiodothyronine and free thyroxine concentrations, bone mineraldensity, 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.

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