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 [1, 2, 3]	SGLT2 inhibitors, e.g., empagliflozin, dapagliflozin, canagliflozin	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 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 intra-glomeruli 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 of these drugs are not recommended when eGFR <45 mL/ml/1.73 m^2 Contrary to initial concerns, the risk of urinary tract infection and acute kidney injury is 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	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	Nausea, vomiting, indigestion

				pancreatic beta cell function.	(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]	
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 m^2) Randomized controlled trial	Blood pressure reduction to <130 mmHg (systolic) and 70-80 mmHg (diastolic)	Among patients at high 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

			evidence lacking for evidence of benefit in MASH			
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 concentrations 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.	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)

					(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	
Thyroid hormone receptor-beta agonists [21] (MAESTRO clinical program**)	Resmetirom	Acts as selective 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.

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