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Review

Metabolic Syndrome and Pharmacological Interventions in Clinical Development

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Abstract: Metabolic syndrome prevalence is between 24 and 27% and poses a significant risk for the development of atherosclerotic cardiovascular disease (ASCVD), type 2 diabetes (T2D), or other comorbidities. Currently, no drugs are approved for metabolic syndrome treatment itself, so the risk factors are treated with therapies approved for cardiac and metabolic conditions. These are approved drugs for dyslipidemia treatment such as statins and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, cornerstone antihypertensive drugs, or novel class glucagon-like peptide 1 (GLP-1) receptor agonists (GLP-1 RA) for T2D and overweight or obesity treatment. We have also evaluated new pharmacological interventions in clinical development that have reached Phase 2 and/or Phase 3 randomized clinical trials (RCTs) for the management of the risk factors of metabolic syndrome. In the pipeline are glucose-dependent insulinotropic polypeptide (GIP), GLP-1, glucagon receptor (GCGR), amylin agonists, and a combination of the latter for T2D and overweight or obesity treatment. Non-entero-pancreatic hormone-based therapies such as ketohexokinase (KHK) inhibitor, growth differentiation factor 15 (GDF15) agonists, monoclonal antibodies (mAbs) as activin type II receptors (ActRII) inhibitors, and a combination of anti-α-myostatin (GFD8) and anti-Activin-A (Act-A) mAbs have also reached Phase 2 or 3 RCTs in the same indications. Rilparencel (Renal Autologous Cell Therapy) is being evaluated in patients with T2D and chronic kidney disease (CKD) in a Phase 3 trial. For dyslipidemia treatment, novel PCSK9 inhibitors (oral and subcutaneous) and cholesteryl ester transfer protein (CETP) inhibitors are in the final stages of clinical development. There is also a surge of a new generation of an antisense oligonucleotide (ASO) and small interfering RNA (siRNA)-targeting lipoprotein(a) [Lp(a)] synthesis pathway that could possibly contribute to a further step forward in the treatment of dyslipidemia. For resistant and uncontrolled hypertension, aldosterone synthase inhibitors and siRNAs targeting angiotensinogen (AGT) messenger RNA (mRNA) are promising new therapeutic options. It would be interesting if a few drugs in clinical development for metabolic syndrome such as 6-bromotryptophan (6-BT), vericiguat, and INV-202 as a peripherally-acting CB1 receptor (CB1r) blocker would succeed in finally gaining the first drug approval for metabolic syndrome itself.

Keywords: metabolic syndrome; pharmacological interventions; research

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1. Introduction

Metabolic syndrome encompasses several inter-related risk factors for the development of atherosclerotic cardiovascular disease (ASCVD), type 2 diabetes (T2D), and other various comorbidities (i.e., risk of cancer, cognitive impairment, non-alcoholic fatty liver disease (NAFLD)) [1,2]. Metabolic risk factors consist of atherogenic dyslipidemia (i.e., increased low-density lipoprotein cholesterol [LDL-C], decreased high-density lipoprotein cholesterol [HDL-C], increased levels of triglycerides), arterial hypertension, hyperglycemia, a prothrombotic state, and a proinflammatory state. Central obesity (particularly

visceral adiposity) and insulin resistance represent underlying risk factors, while sedentary lifestyle, aging, hormonal imbalance, and genetic or ethnic predisposition represent other associated conditions [1]. The International Diabetes Federation (IDF) and the American Heart Association/National Heart, Lung, and Blood Institute (AHA/NHLBI) constitute the diagnosis of metabolic syndrome as the presence of any three out of five individual risk factors: elevated waist circumference, dyslipidemia (i.e., elevated triglycerides and decreased HDL-C), elevated blood pressure, and elevated fasting glucose (Table 1) [3].

Table 1. Definition of metabolic syndrome [3].

Measure	Categorical Cut Points
Elevated waist circumference *	Population- and country-specific definitions
Elevated triglycerides (drug treatment for elevated triglycerides is an alternate indicator **)	≥150 mg/dL (1.7 mmol/L)
Reduced HDL-C (drug treatment for reduced HDL-C is an alternate indicator **)	<40 mg/dL (1.0 mmol/L) in males; <50 mg/dL (1.3 mmol/L) in females
Elevated blood pressure (antihypertensive drug treatment in a patient with a history of hypertension is an alternate indicator)	Systolic ≥ 130 and/or diastolic ≥ 85 mm Hg
Elevated fasting glucose *** (drug treatment of elevated glucose is an alternate indicator)	≥100 mg/dL

HDL-C (high-density lipoprotein cholesterol). * It is recommended that the IDF cut-points be used for non-Europeans and either the IDF or AHA/NHLBI cut-points used for people of European origin until more data are available. ** The most commonly used drugs for elevated triglycerides and reduced HDL-C are fibrates and nicotinic acid. A patient taking 1 of these drugs can be presumed to have high triglycerides and low HDL-C. High dose of ω-3 fatty acids presumes high triglycerides. *** Most patients with type 2 diabetes mellitus will have metabolic syndrome by the proposed criteria.

The prevalence of metabolic syndrome in the general population is between 24 and 27% [4,5]. The MetS-Greece study reported that among individuals with metabolic syndrome, abdominal obesity (72%) was the most common abnormality. The prevalence of arterial hypertension (66%), elevated glucose (including patients with diabetes mellitus) (53%), elevated triglyceride levels (62%), and low HDL-C levels (54%) was ineligibly lower [5].

The goal of metabolic syndrome management is to reduce the risk of ASCVD and T2D development. If ASCVD or T2D are present components of metabolic syndrome, they contribute to further disease progression and risk. First-line interventions for lowering long-term and short-term risk consist of non-pharmacological interventions through lifestyle modifications (i.e., diet, exercise, weight loss, tobacco cessation) [1]. Surgical treatment strategies such as bariatric surgery can also be an option for weight loss management [6]. In individuals with a higher 10-year risk assessment of cardiovascular disease (CVD) risk on the Framingham scoring [7], pharmacological management for particular metabolic risk factors must be considered. Since metabolic syndrome lacks a single etiological factor or central pathophysiological abnormality, multiple specific pathways are targeted with several drug classes [1]. The choice of therapeutic approach depends on the individual risk factors of a patient. Currently, no drugs are approved for metabolic syndrome indication itself. Instead, metabolic syndrome risk factors are treated with therapies approved for cardiac and metabolic conditions. These treatments affect several different pathways associated with metabolic syndrome. There are several pharmacological approaches and drug classes for the management of each of the risk factors of metabolic syndrome.

1.1. Atherogenic Dyslipidemia

Atherogenic dyslipidemia can be modulated with statin or non-statin therapy. The primary goal for that treatment is an elevated LDL-C level, but in a case of very high (≥500 mg/dL) triglycerides, they should be the first priority. Statins, 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase inhibitors, are the cornerstone for dyslipi-

demia management. There are seven different statins approved by the Food and Drug Administration (FDA). They are atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, and simvastatin. They are additionally subdivided to low, moderate, and high intensity LDL-C, lowering the therapy depending on the type and the dose of a particular statin [8]. Non-statin therapies that may be useful in combination with statin therapy include ezetimibe (inhibits cholesterol absorption at the brush border of the small intestine mediated by the sterol transporter Niemann-Pick C1-Like-1 (NPC1L1)), bile acid sequestrants (colesevelam, colestipol, and cholestyramine), and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors (alirocumab, evolocumab, and inclisiran). Alirocumab and evolocumab are PCSK9 inhibitor monoclonal antibodies (mAbs), while inclisiran is a small interfering RNA (siRNA) targeting PCSK9 messenger RNA (mRNA) [9,10]. Triglyceride-lowering drugs, nicotinic acid, and fibrates (fenofibrate, fenofibric acid, gemfibrozil) may be useful in some patients with severe hypertriglyceridemia [2]. Cholesteryl ester transfer protein (CETP) inhibitors (torcetrapib, dalcetrapib, evacetrapib, anacetrapib, TA-8995) have been tested in several randomized clinical trials (RCTs) but still without proven clinical benefit or off-target effects [11,12]. Bempedoic acid, an ATP citrate lyase inhibitor, demonstrated a lower risk of major adverse cardiovascular events (MACE) among statin-intolerant patients [13].

1.2. Arterial Hypertension

For elevated blood pressure, five major drug classes are available as a first-line antihypertensive treatment. A thiazide/thiazide-like diuretic, calcium channel blocker (CCB), angiotensin-converting enzyme inhibitor (ACEi), angiotensin receptor blocker (ARB), or beta-blocker (BB) can be used depending on the individual patient risk profile. Blockers of the renin–angiotensin system (RAS) (ACEi or ARB) are considered as a common component of the general combination treatment strategy, while BBs are restricted to special clinical conditions or situations. Compelling or possible contraindications for the selection of drug classes should be evaluated when prescribing first-line antihypertensive treatment. Other antihypertensive drugs (alpha-blockers, centrally acting agents and mineralocorticoid-receptor antagonists (MRAs)) can be prescribed in some specific cases, or when blood pressure cannot be controlled by various combinations of the major drug classes [14].

1.3. Management of Hyperglycemia

There are eight classes of antihyperglycemic drugs; bigvanides (metformin), sulfonylurea (second generation particularly), thiazolidinediones (pioglitazone), dipeptidyl peptidase-4 (DPP-4) inhibitors (i.e., alogliptin, vildagliptin, sitagliptin, linagliptin, saxagliptin), insulins, sodium/glucose co-transporter 2 (SGLT-2) inhibitors (i.e., canagliflozin, dapagliflozin, empagliflozin), glucagon-like peptide 1 (GLP-1) receptor agonists (GLP-1 RAs) (i.e., dulaglutide, liraglutide, semaglutide), dual glucose-dependent insulinotropic polypeptide (GIP), and GLP-1 RA (tirzepatide), which are commonly used for hyperglycemia management in T2D. α-Glucosidase inhibitors are less commonly used, while other glucose-lowering medications (i.e., meglitinides, colesevelam, quick-release bromocriptine, and pramlintide) are rarely used [15]. Metformin is a pharmacological option in particular individuals with prediabetes, those with BMI $\geq$ 35 kg/m^2, those aged < 60 years, and women with prior gestational diabetes mellitus [16].

1.4. Weight Management

It is estimated that 40% of Americans suffer from obesity and 20% are overweight [17]. There are six different drug classes approved by the FDA for the treatment of obesity: orlistat, phentermine/topiramate extended release (ER), naltrexone/bupropion ER, liraglutide 3 mg, semaglutide 2.4 mg, and tirzepatide [18,19]. Incretin drugs, particularly GLP-1 RA, have revolutionized the treatment of obesity. They can help patients suffering from obesity to lose ~20 to 25% of their body weight [17].

In addition to approved drug classes that can be used in metabolic syndrome management, other targets have come up formerly in research: the so-called master metabolic regulators. They included the pathways activated by the insulin receptors, adenosine monophosphate (AMP) kinase, inflammatory cascades, endocannabinoid receptors, nuclear receptors, glucocorticoids, and mitochondrial oxidative pathways [20]. From a drug development perspective, it is problematic to conduct a clinical trial solely for metabolic syndrome [21]. As mentioned before, the metabolic syndrome risk factors are treated with therapies approved for cardiac and metabolic conditions. The questions arises as to what a comparator would be and if it is ethical to use placebo. What particular drug target could provide the highest benefit? What clinical endpoint should be used, MACE or a surrogate endpoint? Despite challenges, the metabolic syndrome risk factors are successfully treated with available pharmacological approaches.

In order to evaluate what is in the pipeline and what can be promising as potential new therapies for metabolic syndrome risk factors management, we have researched the most relevant clinical trials database.

2. Material and Methods

We have decided to research the ClinicalTrials.gov database as the most comprehensive RCTs database. ClinicalTrials.gov lists over 300,000 research studies, while the second biggest EU Clinical Trials Register lists over 34,000 clinical trials [22]. Further on, relevant RCTs that evaluate new substances that can potentially be a new standard of care are mostly multicenter and are evaluated in USA, Europe, and other parts of the world. Therefore, ClinicalTrials.gov should capture all RCTs of interest. On 13 May 2024, we have researched ClinicalTrials.gov for the records that fulfill several criteria: Phase 2 and Phase 3 RCTs, interventional RCTs, RCTs that are in recruiting, active-non recruiting, and completed phases, RCTs conducted only in adult population (>18), and with study start from 5 May 2021 to 5 May 2024. The search terms were "Metabolic syndrome", "Prediabetes", "Insulin resistance", "Obesity/Overweight", "Type 2 diabetes", "Hyperlipidemia", "Dyslipidemia", "Lipoprotein Disorder", and "Hypertension".

We have not included Phase 1 trials in our research since only 13.8% of Phase 1 trials reach drug approval [23]. Therefore, we have decided to go for Phase 2 and Phase 3 trials. Sponsors usually conducts interim analysis of RCTs that are active (in progress), and based on the given results they decide on proceeding or stopping the drug development program. Therefore, we have agreed that a three-year timeframe is long enough to catch all drugs in development that may be potential candidates to obtain drug approval. Some RCTs are conducted in parallel in more than one phase (i.e., Phase 1 and Phase 2a). In that case, we have included these studies into our research if they fulfill at least one "phase" inclusion criteria. We have excluded RCTs evaluating already known herbal remedies (i.e., herbal medicine used in traditional medicine but evaluated in RCTs in a new indication). Herbal medicines are mostly less potent and less selective than drugs themselves, and there are very small chances that an already known herbal medicine would become a new therapeutic option in metabolic syndrome treatment. We have also excluded RCTs evaluating already approved drugs used in a risk-factor treatment (e.g., inclisiran, semaglutide, tirezpatide, etc.) and RCTs in other indications/comorbidities that are not closely related to keywords of interest for metabolic syndrome (i.e., pulmonary arterial hypertension, ocular hypertension, non-alcoholic fatty liver disease (NAFLD)). The flowchart diagram of the research is present in Figure 1. Data have been extracted into the predesigned Microsoft Excel (ver. 2311, Microsoft, Redmond, WA, USA) spreadsheet.

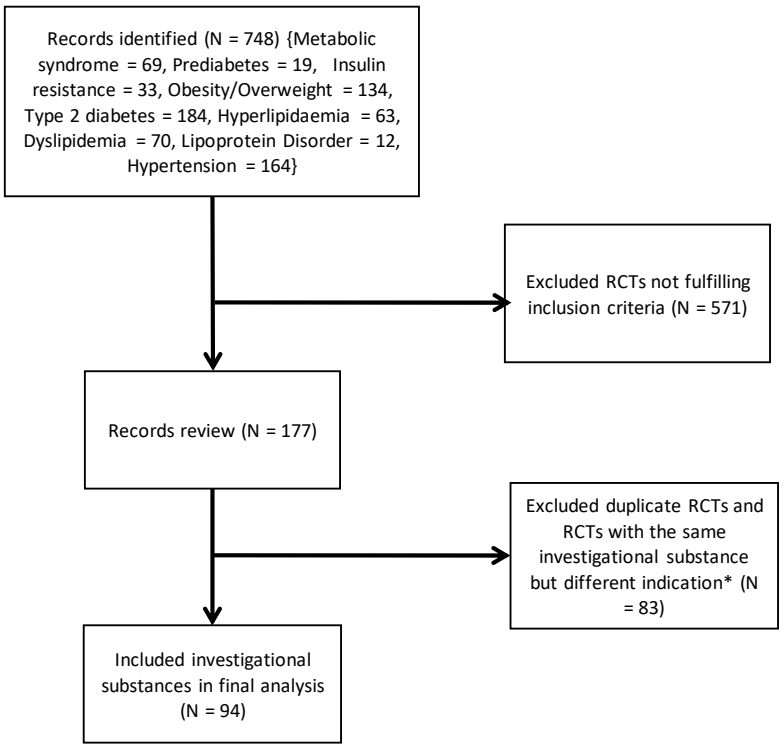

Figure 1. Flow chart diagram. * RCTs that are evaluating the same investigational substance in different indications are summarized into one record, which documented all indications for which it is in research.

3. Results

We have identified 748 records in our research. The majority of the records are for T2D and hypertension, while metabolic syndrome has 69 records (Figure 1). After selection, we have detected 94 new investigational drugs that are in the pipeline for metabolic syndrome risk factors' management (Table 2).

Half (51%) of investigational drugs have reached Phase 3 RCTs, and the other half (49%) are in a Phase 2 RCT. We have identified that the most investigational drugs are evaluated in RCTs which main clinical trials sites are located in United States of America (USA) and/or Europe (60%), less in China or South Korea (37%), and a negligible number in Brazil (1%). RCTs with main clinical trials located in USA and/or Europe and in China are represented with 2%. We could not find any information on the mechanism of action for 17 (18%) investigational drugs, of which 15 (88%) were tested in China or South Korea, 1 (6%) in Brazil, and 1 (6%) in USA and/or Europe. From all investigational drugs evaluated in the main trial sites located in China or South Korea, for 43% of them we could not find mechanism of action of investigational drugs.

Most investigational drugs are evaluated in T2D (41%), obesity and/or overweight (31%), dyslipidemia and/or hyperlipidemia and/or lipoprotein disorder (29%), and hypertension (19%) indications (Table 2).

Table 2. Pharmacological interventions in clinical development.

N	Investigational Drug	Mechanism of Action	Indication	Main Site Location	Phase	NCT
1	6-bromotryptophan (6-BT)	Endogenous plasma microbiome-derived tryptophan metabolite	Metabolic Syndrome	USA and/or Europe	Phase 1 Phase 2	NCT05971524
2	AD-209	N/A	Essential Hypertension	South Korea	Phase 2	NCT05631990
3	AD-218	N/A	Dyslipidemia	South Korea	Phase 3	NCT05631990
4	AD-221 and AD-221A	N/A	Primary Hypercholesterolemia	China	Phase 3	NCT05131997
5	AD-223	N/A	Essential Hypertension	South Korea	Phase 3	NCT06052748
6	ALN-KHK	RNAi targeting ketohexokinase	Type 2 Diabetes Mellitus with Obesity	USA and/or Europe	Phase 1 Phase 2	NCT05761301
7	ALT-801 (SP-1373)	Dual GCGR and GLP-1 receptor agonist	Obesity	USA and/or Europe	Phase 2	NCT05295875
8	AP-325	Binds and modulates the GABAA receptor (an ionotropic receptor and ligand-gated ion channel)	Type 2 Diabetes Mellitus	USA and/or Europe	Phase 2	NCT05160272
9	APHD-012	Distal jejunal-release dextrose	Obesity	USA and/or Europe	Phase 2	NCT05385978
10	ATB-1011 and ATB-1012	N/A	Essential Hypertension and Type 2 Diabetes Mellitus	China	Phase 3	NCT05573477
11	AZD0780	Oral PCSK9 Inhibitor	Dyslipidemia	USA and/or Europe	Phase 2	NCT06173570
12	AZD8233	ASO targeting PCSK9	Hyperlipidaemia	USA and/or Europe	Phase 2	NCT04964557, NCT06173570
13	AZD9550	Dual GCGR and GLP-1 receptor agonist	Type 2 Diabetes Mellitus with Overweight or Obesity	USA and/or Europe	Phase 1 Phase 2	NCT06151964
14	Baxdrostat (CIN-107)	Aldosterone synthase inhibitors	Uncontrolled Hypertension and Resistant Hypertension; Uncontrolled Hypertension and Chronic Kidney Disease	USA and/or Europe	Phase 2 Phase 3	NCT06344104, NCT05432167
15	BC Lispro (THDB0206)	Insulin	Type 2 Diabetes Mellitus	China	Phase 3	NCT05834868
16	Berlim 25/2	N/A	Type 2 Diabetes Mellitus and Dyslipidemia	Brazil	Phase 3	NCT04602754

Table 2. *Cont.*

N	Investigational Drug	Mechanism of Action	Indication	Main Site Location	Phase	NCT
17	Bimagrumab	mAb inhibitor of ActRII	Overweight or Obesity	USA and/or Europe	Phase 2	NCT05616013
18	BMF-219	Oral irreversible covalent inhibitor of menin	Type 2 Diabetes Mellitus	USA and/or Europe	Phase 1 Phase 2	NCT05731544
19	BR1017A and BR1017B	N/A	Essential Hypertension and Primary Hypercholesterolemia	South Korea	Phase 3	NCT05930028
20	BR1018B and BR1018C	N/A	Essential Hypertension and Primary Hypercholesterolemia	South Korea	Phase 3	NCT06165250
21	Cagrilintide	Amylin receptor agonist	Type 2 Diabetes Mellitus; Overweight or Obesity	USA and/or Europe	Phase 2 Phase 3	NCT05813925, NCT04982575
22	CKD-391 and CKD-331	N/A	Primary Hypercholesterolemia	China, South Korea	Phase 3	NCT05657574
23	CPL207280	GPR40 (also known as FFA receptor 1) agonist	Type 2 Diabetes Mellitus	USA and/or Europe	Phase 2	NCT05248776
24	D064 and D702	N/A	Essential Hypertension	South Korea	Phase 3	NCT06121518
25	D150, D745 and D759	N/A	Type 2 Diabetes Mellitus	South Korea	Phase 3	NCT05566028
26	Dapiglutide	Dual GLP-1R/GLP-2R agonist	Obesity	USA and/or Europe	Phase 2	NCT05788601
27	Denatonium Acetate (ARD-101)	Oral potential TAS2R agonist	Obesity	USA and/or Europe	Phase 2	NCT05121441
28	DW1125 and DW1125A	N/A	Primary Hypercholesterolemia or Dyslipidemia	South Korea	Phase 3	NCT05970679
29	DWP16001	SGLT2 inhibitor	Type 2 Diabetes Mellitus	China, South Korea	Phase 3	NCT05376930, NCT05505994
30	Ecnoglutide (XW003)	Long-acting cAMP Signaling Biased GLP-1 Analog	Obesity; Type 2 Diabetes Mellitus	USA and/or Europe, China	Phase 2 Phase 3	NCT05111912, NCT05813795, NCT05680155, NCT05680129
31	Efsitora Alfa (BIF, LY3209590, or insulin efsitora alfa)	Basal Insulin Fc	Type 2 Diabetes Mellitus	USA and/or Europe	Phase 3	NCT05462756

Table 2. *Cont.*

N	Investigational Drug	Mechanism of Action	Indication	Main Site Location	Phase	NCT
32	GLY-200	Mucin-complexing polymer	Obesity; Type 2 Diabetes Mellitus	USA and/or Europe	Phase 2	NCT06259981, NCT05478525
33	GSBR-1290	Oral GLP-1 receptor agonist	Type 2 Diabetes Mellitus, and Overweight or Obesity	USA and/or Europe	Phase 1 Phase 2	NCT05762471
34	GZR18	GLP-1 receptor agonist	Type 2 Diabetes Mellitus; Overweight or Obesity	China	Phase 1 Phase 2	NCT06256523, NCT06256536, NCT06256562
35	GZR4	INSR agonist	Type 2 Diabetes Mellitus	China	Phase 2	NCT06202079
36	HCP1803	N/A	Essential Hypertension	South Korea	Phase 3	NCT05362110
37	HCP1904-3	N/A	Essential Hypertension	South Korea	Phase 3	NCT05199129
38	HCP2102	N/A	Essential Hypertension	South Korea	Phase 3	NCT05450601
39	HD-6277	Selective GPR40 agonist	Type 2 Diabetes Mellitus	South Korea	Phase 2	NCT05666128
40	HEC88473	Dual FGF21 receptor and GLP-1 receptor agonist	Type 2 Diabetes Mellitus	China	Phase 2	NCT06148649
41	HRS9531	Dual GIP and GLP-1 receptor agonist	Obesity; Type 2 Diabetes Mellitus	China	Phase 2	NCT05881837, NCT05966272
42	HS-20094	Dual GIP and GLP-1 receptor agonist	Type 2 Diabetes Mellitus; Overweight or Obesity	China	Phase 2	NCT06118008, NCT06118021
43	HSG4112	Analog of glabridin	Overweight or Obesity	South Korea	Phase 2	NCT05197556
44	iGlarLixi vs. IDegAsp	Insulins	Type 2 Diabetes Mellitus	China	Phase 3	NCT05413369
45	INS068	Long-acting insulin analog	Type 2 Diabetes Mellitus	South Korea	Phase 3	NCT05702073, NCT05699408
46	Insulin Efsitora Alfa (LY3209590)	Basal Insulin Fc (BIF)	Type 2 Diabetes Mellitus	USA and/or Europe	Phase 3	NCT05662332, NCT05275400
47	INV-202	CB1R inverse agonist	Obesity and Metabolic Syndrome; Type 2 Diabetes Mellitus	USA and/or Europe	Phase 2	NCT05891834, NCT05514548

Table 2. *Cont.*

N	Investigational Drug	Mechanism of Action	Indication	Main Site Location	Phase	NCT
48	ION904 (IONIS-AGT-LRx)	Hepatocyte-directed ASO targeting AGT mRNA	Uncontrolled Hypertension	USA and/or Europe	Phase 2	NCT05314439
49	JS002	Humanized anti-PCSK9 mAb	Hyperlipidaemia	China	Phase 3	NCT05532800
50	JW0101+C2101	Livalo (pitavastatin)	Dyslipidemia and Hypertension	South Korea	Phase 3	NCT05331014
51	JW0201	N/A	Type 2 Diabetes Mellitus	South Korea	Phase 3	NCT05814393
52	Lepodisiran (LY3819469)	siRNA (binds to the hepatic asialoglycoprotein receptor) targeting Lp(a)	Elevated Lipoprotein(a)	USA and/or Europe	Phase 2 Phase 3	NCT05565742, NCT06292013
53	Lerodalcibep (LIB003)	PCSK9 Inhibitor	Hyperlipidaemia and High risk Cardiovascular Disease (CVD)	USA and/or Europe	Phase 3	NCT05004675, NCT05234775
54	Lorundrostat (MLS-101)	Aldosterone synthase inhibitor	Resistant Hypertension; Uncontrolled Hypertension	USA and/or Europe	Phase 2 Phase 3	NCT06153693, NCT05968430, NCT05001945
55	Eloralintide (LY3841136)	Amylin receptor agonist	Overweight or Obesity	USA and/or Europe	Phase 2	NCT06230523
56	MAR001	Maresin 1 (MaR1) specialised pro-resolving lipid mediator	Metabolic dysfunction at screening (triglyceride levels > 2.8 mmol/L)	USA and/or Europe	Phase 1 Phase 2	NCT05896254
57	Maridebart cafraglutide (AMG 133)	Dual GIP and GLP-1 receptor agonist	Overweight or Obesity With or Without Type 2 Diabetes Mellitus	USA and/or Europe	Phase 2	NCT05669599
58	Mazdutide (IBI362, LY3305677)	Dual GCGR and GLP-1 receptor agonist	Type 2 Diabetes Mellitus with Obesity; Overweight or Obesity	USA and/or Europe, China	Phase 2 Phase 3	NCT06184568, NCT06143956, NCT04904913
59	MBL949	GDF15 agonist (agonist at the GFRAL/RET receptor)	Obesity with or without Type 2 Diabetes Mellitus	USA and/or Europe	Phase 2	NCT05199090
60	MK-0616	Oral PCSK9 inhibitor	Hyperlipidaemia	USA and/or Europe	Phase 3	NCT05952856
61	Muvalaplin (LY3473329)	Orally active inhibitor of Lp(a)	Elevated Lipoprotein(a) at High Risk for Cardiovascular Events	USA and/or Europe	Phase 2	NCT05563246
62	NNC0165-1875	NPY2R or Y2R agonist	Obesity	USA and/or Europe	Phase 2	NCT04969939
63	NNC0480-0389	N/A	Type 2 Diabetes Mellitus	USA and/or Europe	Phase 2	NCT05144984

Table 2. *Cont.*

N	Investigational Drug	Mechanism of Action	Indication	Main Site Location	Phase	NCT
64	NNC0519-0130	Dual GIP and GLP-1 receptor agonist	Overweight or Obesity, Type 2 Diabetes Mellitus	USA and/or Europe	Phase 2	NCT06326060, NCT06326047
65	NST-1024 (SEFA-1024)	CETP inhibitor	Hypertriglyceridemia	USA and/or Europe	Phase 2	NCT05889156
66	Obicetrapib (AMG-899, DEZ-001, TA-8995)	CETP inhibitor	Hyperlipidaemia; Heterozygous familial hypercholesterolemia (HeFH) and/or atherosclerotic cardiovascular disease (ASCVD) or multiple ASCVD risk factors	USA and/or Europe	Phase 2 Phase 3	NCT05421078, NCT06005597, NCT05266586
67	Ocedurenone(KBP-5074)	Third-generation non-steroidal MRA	Uncontrolled Hypertension and Moderate or Severe Chronic Kidney Disease	USA and/or Europe	Phase 3	NCT04968184
68	Olezarsen (ISIS 678354, AKCEA-APOCIII-LRx)	ASO targeting mRNA for APOC3	Hypertriglyceridemia and Atherosclerotic Cardiovascular Disease, or With Severe Hypertriglyceridemia; Severe Hypertriglyceridemia	USA and/or Europe	Phase 3	NCT05552326, NCT05079919, NCT05610280
69	Olpasiran (AMG-890, ARO-LPA)	siRNA (binds to the hepatic asialoglycoprotein receptor) targeting Lp(a)	Atherosclerotic cardiovascular disease (ASCVD) and elevated Lipoprotein(a).	USA and/or Europe	Phase 3	NCT05581303
70	Orforglipron (LY3502970)	Non-peptide GLP-1 receptor agonist	Type 2 Diabetes Mellitus with Overweight or Obesity; Type 2 Diabetes Mellitus; Overweight or Obesity and related comorbidities, Overweight or Obesity	USA and/or Europe	Phase 3	NCT05803421, NCT06010004, NCT05869903, NCT05872620, NCT05051579, NCT05048719
71	PB-201	Glucokinase activator (partial, pancreas- and liver-dual activator of glucokinase)	Type 2 Diabetes Mellitus	China	Phase 3	NCT05102149
72	Pegozafermin (BIO89-100)	FGF21 analog	Severe Hypertriglyceridemia	USA and/or Europe	Phase 3	NCT05852431

Table 2. *Cont.*

N	Investigational Drug	Mechanism of Action	Indication	Main Site Location	Phase	NCT
73	Pelacarsen (IONIS-APO(a)-LRx, AKCEA-APO(a)-LRx, or TQJ230)	Apo(a) inhibitor, hepatocyte-directed ASO targeting mRNA transcribed from the *LPA* gene	Hyperlipoproteinemia(a) and Established Cardiovascular Disease	USA and/or Europe	Phase 3	NCT05305664, NCT05900141
74	Pemafibrate (K-877, LY3473329)	Selective peroxisome proliferator-activated receptor (PPAR)-α modulator (SPPARM)	Hypercholesterolemia and statin intolerance; Elevated Lipoprotein(a)	USA and/or Europe	Phase 2 Phase 3	NCT05923281, NCT05563246
75	Plozasiran (ARO-APOC3)	siRNA targeting mRNA for APOC3	Hypertriglyceridemia; Severe Hypertriglyceridemia; Dyslipidemia	USA and/or Europe	Phase 2 Phase 3	NCT06347133, NCT06347016, NCT05413135, NCT04720534, NCT04998201
76	RAY1225	Dual GIP and GLP-1 receptor agonist	Type 2 Diabetes Mellitus; Obesity	China	Phase 2	NCT06254274, NCT06254261
77	Recaticimab (SHR-1209)	mAb against PCSK9	Hyperlipidaemia	China	Phase 3	NCT04885218
78	Rilparencel (Renal Autologous Cell Therapy-REACT®)	Renal Autologous Cell Therapy	Type 2 Diabetes Mellitus and Chronic Kidney Disease	USA and/or Europe	Phase 3	NCT05099770
79	Retatrutide (LY3437943)	Triple GIP, GLP-1 and GCGR receptor agonist	Overweight or Obesity and Chronic Kidney Disease With or Without Type 2 Diabetes Mellitus; Type 2 Diabetes Mellitus; Overweight or Obesity; Type 2 Diabetes Mellitus with Overweight or Obesity; Overweight or Obesity with Cardiovascular Disease	USA and/or Europe	Phase 2 Phase 3	NCT05936151, NCT06297603, NCT05929066, NCT05929079, NCT05882045, NCT04881760
80	RGT-075	Oral GLP-1 receptor agonist	Overweight or Obesity	USA and/or Europe	Phase 2	NCT06277934
81	Solbinsiran (LY3561774)	siRNA that targets ANGPTL3	Dyslipidemia	USA and/or Europe	Phase 2	NCT05256654
82	SPC1001	N/A	Essential Hypertension	South Korea	Phase 2	NCT06212648
83	SPH3127	Renin inhibitor (direct)	Essential Hypertension	China	Phase 3	NCT05359068

Table 2. *Cont.*

N	Investigational Drug	Mechanism of Action	Indication	Main Site Location	Phase	NCT
84	Supaglutide	GLP-1 receptor agonist	Type 2 Diabetes Mellitus	China	Phase 2 Phase 3	NCT04994288, NCT04998032
85	Survodutide (BI 456906)	Dual GCGR and GLP-1 receptor agonist	Type 2 Diabetes Mellitus with Overweight or Obesity; Obesity; Overweight or Obesity	USA and/or Europe	Phase 3	NCT06066528, NCT06176365, NCT06066515, NCT06077864
86	TLC-3595 (S-723595)	Allosteric inhibitor of acetyl-CoA carboxylase 2 (ACC2)	Insulin Resistance	USA and/or Europe	Phase 2	NCT05665751
87	Trevogrumab (REGN1033) and Garetosmab (REGN2477)	Trevogrumab is GFD8 fully humanized mAb, Garetosmab (REGN2477) Act-A mAb	Obesity	USA and/or Europe	Phase 2	NCT06299098
88	Vericiguat	Stimulator of soluble guanylate cyclase (sGC)	Metabolic Syndrome and Coronary Vascular Dysfunction	USA and/or Europe	Phase 2	NCT05711719
89	VK2735	Dual GIP and GLP-1 receptor agonist	Overweight or Obesity	USA and/or Europe	Phase 2	NCT06068946
90	XXB750	mAb, NPR1 agonist	Resistant Hypertension	USA and/or Europe	Phase 2	NCT05562934
91	Yogliptin	DPP-4 inhibitor	Type 2 Diabetes Mellitus	China	Phase 3	NCT05318326
92	Zerlasiran (SLN360)	siRNA (binds to the hepatic asialoglycoprotein receptor) targeting Lp(a)	Elevated lipoprotein(a) at high risk of atherosclerotic cardiovascular disease events	USA and/or Europe	Phase 2	NCT05537571
93	Zilebesiran (ALN-AGT)	siRNA targeting AGT mRNA	High cardiovascular risk and Uncontrolled Hypertension; Hypertension	USA and/or Europe	Phase 2	NCT06272487, NCT04936035, NCT05103332
94	Zodasiran (ARO-ANG3)	siRNA that targets ANGPTL3	Dyslipidemia	USA and/or Europe	Phase 2	NCT04832971

ACC2: acetyl-CoA carboxylase 2; Act-A: Activin-A; ActRII: activin type II receptors; AGT: angiotensinogen; ANGPTL3: angiopoietin-like protein 3; Apo(a): apolipoprotein(a); APOC3: apolipoprotein C-III; ASO: antisense oligonucleotide; CB1R: Cannabinoid receptor-1; CETP: cholesteryl ester transfer protein; FGF21: fibroblast growth factor 21; GCCR: glucagon receptor; GDF15: growth differentiation factor 15; GFD8: α-myostatin; GIP: glucose-dependent insulinotropic polypeptide; GLP-1: glucagon-like peptide 1; GPR40: class A G-protein coupled receptor (GPCR); INSR: insulin receptor; KHK: ketohexokinase; Lp(a): lipoprotein(a) gene; mAbs: monoclonal antibodies; MRA: mineralocorticoid-receptor antagonists; N/A: not applicable; NPR1: natriuretic peptide receptor 1; NPY2R: neuropeptide Y receptor type 2; PCSK9: proprotein convertase subtilisin/kexin type 9; SGLT2: Sodium-glucose cotransporter-2; siRNA: small interfering RNA; TAS2R: Bitter Taste Receptor.

3.1. Type 2 Diabetes, Obesity and/or Overweight

In T2D, obesity, and/or overweight treatment, new entero-pancreatic hormone-based pharmacotherapies are under development. Ecnoglutide (XW003) is a long-acting GLP-1 RA administered as a once-weekly injection that has demonstrated positive results in a Phase 2 trial in Chinese patients with T2D [24]. The dual glucagon receptor (GCGR) and GLP-1 receptor agonists AZD9550, mazdutide (IBI362, LY3305677) [25], maridebart cafraglutide (AMG 133), and survodutide (BI 456906) [26] are strengthening the pipeline for the incretin pathway in obesity or overweight treatment with or without T2D. In addition to the approved tirzepatide [27], other dual GIP and GLP-1 receptor agonists, HRS9531, HS-20094, and RAY1225 are being evaluated in China in patients with obesity or T2D. NNC0519-0130 is also under development in the USA and/or Europe. Retatrutide (LY-3437943) is a triple GIP, GLP-1, and GCGR agonist that is tested in several indications (overweight or obesity and chronic kidney disease with or without T2D, T2D, obesity or overweight, T2D with obesity or overweight, obesity or overweight with cardiovascular disease) (Table 2) [28]. Cagrilintide and eloralintide (LY3841136) as amylin receptor agonists are evaluated in T2D or obesity/overweight indications (Table 2). Amylin is involved in postprandial satiety regulation. Cagrilintide, as a new long-acting amylin analog, is combined with semaglutide 2.4 mg once weekly (CagriSema) in patient with obesity [29]. NNC0165-1875 is a neuropeptide Y receptor type 2 agonist (NPY2R agonist or Y2R agonist) and has finished the Phase 2 trial but with no results posted for now. Y2R inhibits food intake by acting centrally on the hypothalamus [30].

Also, the new non-entero-pancreatic hormone-based pharmacotherapy is in clinical development. Oral denatonium acetate (ARD-101) is a potential bitter taste receptor (TAS2R) agonist [31] and is being evaluated in obesity treatment in a Phase 2 trial. ALN-KHK belongs to a new treatment approach with siRNA, which is conjugated with a new class of degraders, a triantennary N-acetylgalactosamine (GalNAc). GalNAc is the ligand of the asialoglycoprotein receptor (ASGPR), a lysosomal targeting receptor specifically expressed on liver cells. Conjugation with GalNAc enables the extracellular protein targets to be successfully internalized and delivered into the lysosome for degradation in the liver [32]. ALN-KHK targets ketohexokinase (KHK). It is considered that the inhibition of KHK prevents fructose-induced metabolic dysfunction, such as insulin resistance, de novo lipogenesis (DNL), and hepatic steatosis [33]. Bimagrumab is a human mAb inhibitor of activin type II receptors (ActRII), which consequently stimulates skeletal muscle growth and causes a reduction in fat mass and weight loss [34]. The other different mechanism of action in obesity or T2D treatment is BMF-219, as an oral irreversible covalent inhibitor of menin. Pbk is a serine/threonine protein kinase, essential for high-fat diet induced beta cell proliferation. The menin inhibition disrupts the menin–JunD interaction and augments Pbk transcription [35]. CPL207280 is a GPR40 agonist (also known as an FFA receptor 1 agonist). GPR40 is a class A G-protein coupled receptor (GPCR), the activation of which after a meal ingestion induces the secretion of incretins in the gut, including GLP-1, GIP, and peptide YY (PYY), the latter controlling appetite and glucose metabolism [36]. PYY is also known as an NPY2R agonist (Y2R agonist), since PYY is rapidly cleaved by DPP-4 to its active form (PYY 3-36), which acts on a Y2R [37]. GLY-200 as a mucin-complexing polymer and MBL949 as a growth differentiation factor 15 (GDF15) agonist (agonist at the GFRAL/RET receptor) are also in clinical development. GDF15, which is a non-homeostatic regulator of food intake and body weight, is emerging as having the potential for a new mechanism in obesity treatment. GDF-15 is a stress-induced cytokine, which is expressed in multiple cell types including cardiomyocytes, adipocytes, and macrophages [38]. At the moment, the Phase 2 trial with MBL949 has been completed and we are awaiting publication of the results. Other mAbs under development are trevogrumab (REGN1033) as an α-myostatin (GFD8), fully humanized mAb and the garetosmab (REGN2477) Activin-A (Act-A) mAb. Act-A is a second "myostatin" that appears to be a more important regulator of muscle mass. The addition of garetosmab (anti-Activin A) to trevogrumab (anti-GDF8) is expected to increase thigh muscle volume and decrease fat mass [39]. In the exciting cell and gene

therapy (CGT) field, we have detected the ProKidney's rilparencel (Renal Autologous Cell Therapy-REACT®) that is being evaluated in patients with T2D and chronic kidney disease (CKD) in the Regen-006 Phase 3 trial. The aim of the autologous cellular therapy is not only to slow and stabilize the progression of CKD, but in some cases possibly drive meaningful improvement in kidney function [40].

3.2. Dyslipidemia and Lipoprotein Disorder

For strengthening the already known approach of PCSK9 inhibition in dyslipidemia, AZD0780 and MK-0616 as oral and lerodalcibep (LIB003) as subcutaneous (SC) PCSK9 inhibitors, are in clinical development. AZD8233 is an antisense oligonucleotide (ASO), targeting PCSK9 as well. China is developing JS002 and recaticimab (SHR-1209) as mAbs targeting PCSK9.

In dyslipidemia and lipoprotein disorders, particularly lipoprotein(a) (Lp(a)), we are approaching a new era with two classes of nucleic acid therapeutics, ASOs and siRNAs. Elevated Lp(a) is one of the last untreatable frontiers of cardiovascular risk. Lp(a) is genetically regulated but due to extensive variability in Lp(a) levels between individuals, a potential role for non-genetic factors cannot be disregarded [41]. Lp(a) is produced from the binding of apolipoprotein(a) (apo(a)) to apolipoprotein B (apo B). Silencing the transcription of the *LPA* gene minimizes the mRNA that encodes for apo(a). ASOs and siRNAs are covalently linked with GalNAc which is rapidly cleaved in the liver, allowing the RNA interference therapy to degrade the mRNA that encodes for apo(a). Olezarsen (ISIS 678354, AKCEA-APOCIII-LRx) and pelacarsen (AKCEA-APO(a)-LRx or TQJ230) are ASOs, while lepodisiran (LY3819469), olpasiran, plozasiran (ARO-APOC3), solbinsiran (LY3561774), zerlasiran (SLN360), and zodasiran (ARO-ANG3) are siRNAs targeting the Lp(a) synthesis pathway. Plozasiran, an apolipoprotein (apo) C-III (APOC3) antagonist, is being evaluated in dyslipidemia. Plozasiran is an GalNAc-bound RNA i that targets APOC3 mRNA within the cytoplasm of hepatocytes, resulting in prolonged suppression of apo C-III. In patients with dyslipidemia, plozasiran reduced triglycerides and atherogenic lipoproteins [42,43]. Olezarsen is also an GalNAc-conjugated ASO that targets mRNA for APOC3. Olezarsen is being evaluated in severe hypertriglyceridemia in a Phase 3 trial, after a Phase 2b trial in patients with moderate hypertriglyceridemia and an elevated cardiovascular risk demonstrated encouraging results in the reduction in triglycerides, apo B, and non-HDL cholesterol [44]. Lepodisiran in a Phase 1 trial demonstrated a significant reduction in serum Lp(a) concentrations in patients with elevated Lp(a) [45]. Solbinsiran and zodasiran areangiopoietin like protein 3 (ANGPTL3) inhibitors. ANGPTL3 regulates lipoprotein metabolism by inhibiting lipoprotein and endothelial lipases. It is known that the ANGPTL3 loss-of-function carriers have decreased circulating triglycerides, LDL-C, and HDL-C. In the ARCHES-2 dose-ranging Phase 2b trial, zodisiran decreased atherogenic triglyceride-rich lipoproteins, LDL-C, and total apo B in patients with mixed hyperlipidemia [46]. In the APOLLO Phase 1 trial, zerlasiran demonstrated a reduction in Lp(a) concentrations in patients with elevated Lp(a) and established ASCVD [47]. Muvalaplin (LY3473329) is an orally administered small molecule inhibitor of Lp(a). It demonstrated positive results in a Phase 1 trial and proceeded to a Phase 2 trial in the clinical development [48].

NST-1024 (SEFA-1024) and obicetrapib (AMG-899, DEZ-001, TA-8995) are the new hope for CETP inhibitors in hypertriglyceridemia and dyslipidemia treatment, respectively (Table 2). Results from a completed Phase 2 trial with obicetrapib in patients with dyslipidemia on a high-intensity statin are encouraging [49]. Pemafibrate (K-877, LY3473329) is a selective peroxisome proliferator-activated receptor (PPAR)-α modulator (SPPARM) and offers a new approach to the treatment of hypercholesterolemia and statin intolerance or elevated Lp(a). It is approved for the treatment of hyperlipidemia in Japan due to a favorable risk–benefit ratio [50].

3.3. Hypertension

For the subgroup of patients with metabolic syndrome that have uncontrolled or resistant hypertension, there are currently several drug classes in clinical development. Baxdrostat (CIN-107) and lorundrostat (MLS-101) are aldosterone synthase inhibitors. Baxdrostat (CIN-107) is in a Phase 3 trial and recruiting. Baxdrostat demonstrated positive effect on the reduction in blood pressure in a Phase 2 trial, the BrigHTN trial, in resistant hypertension [51]. However, the HALO (efficacy and safety of baxdrostat in patients with uncontrolled hypertension) trial did not demonstrate a significant blood pressure-lowering benefit of baxdrostat compared to placebo [52]. Lorundrostat is at the moment in a Phase 3 RCT, since the Target-HTN Phase 2 trial demonstrated a significant, double-digit reduction in systolic blood pressure in an uncontrolled hypertension [53]. Ocedurenone (KBP-5074) is a third-generation non-steroidal MRA evaluated in uncontrolled or resistant hypertension and chronic kidney disease [54]. ION904 (IONIS-AGT-L_{Rx}) is an ASO conjugated with GalNAc that inhibits angiotensinogen (AGT) mRNA in hepatocytes. In a Phase 2 trial in patients with uncontrolled hypertension, it significantly reduced plasma AGT levels and reduced blood pressure when given SC monthly [55]. Zilebesiran (ALN-AGT) is also an siRNA conjugated with GalNAc and targeting AGT which has the potential for biannual dosing. Recent KARDIA-2 trial results demonstrated a significant systolic blood pressure reduction in patients with uncontrolled hypertension [56]. XXB750 is a fully humanized mAb long-acting natriuretic peptide receptor 1 (NPR1) agonist. Atrial natriuretic peptide (ANP) induces vasodilation via NPR1 in the vasculature [57]. XXB750 reduced blood pressure in a dose-dependent manner in a Phase 1 trial [58].

3.4. Metabolic Syndrome and Insulin Resistance

For metabolic syndrome treatment itself, 6-bromotryptophan (6-BT) and vericiguat are in Phase 2 trials and recruiting. 6-bromotryptophan (6-BT) is an endogenous plasma microbiome-derived tryptophan metabolite, and vericiguat is a stimulator of soluble guanylyl cyclase. Vericiguat showed favorable results on the reduction of death from any cause or hospitalization for heart failure in patients with high-risk heart failure in the VICTORIA trial [59]. It would be interesting to see its results in an ongoing trial with metabolic syndrome and coronary vascular dysfunction. INV-202 as a peripherally acting CB1 receptor (CB1r) blocker showed promising results on weight loss and biomarkers in metabolic syndrome patients in a Phase 1b trial. It is believed that INV-202 has very low central nervous system (CNS) penetration in contrast to former cannabinoid blockers such as rimonabant, which was compromised with serious neuropsychiatric adverse effects [60,61].

TLC-3595 (formerly S-723595), a small molecule, allosteric inhibitor of acetyl-CoA carboxylase 2 (ACC2), is recruiting patients with insulin resistance in a Phase 2 trial. The inhibition of ACC2 may increase fatty acid oxidation (FAO), reduce ectopic lipid accumulation, and improve insulin sensitivity in skeletal muscle and liver [62,63]. We did not find any relevant RCT for prediabetes treatment.

4. Discussion

The pharmacological treatment of the metabolic syndrome requires a comprehensive approach targeting several different pathways, depending on the individual risk factors of a patient. There is a vast number of available drug classes for cardiac and metabolic conditions treatments, but there is still a need for more efficacious, safe, and more convenient dosing pharmacological options. We have identified that the investigational drugs in our research are tested the most in T2D (41%), obesity and/or overweight (31%), dyslipidemia and/or hyperlipidemia, and/or lipoprotein disorders (29%), and more treatment options will probably emerge in these indications. For some investigational drugs, we could not find a mechanism of action, mostly for the main clinical sites located in China and/or South Korea. It is unknown if these drugs are under development with the new mechanism of action or with the same mechanism of action as approved drugs already on the market (e.g., as like drugs).

SGLT-2 inhibitors and GLP-1 RA have revolutionized T2D treatment, as well as the GLP-1 RA obesity treatment [16–18]. New combinations in entero-pancreatic hormone-based pharmacotherapies are in clinical development, mostly in Phase 3 trials. China is developing the dual GIP and GLP-1 receptor agonists HRS9531, HS-20094, and RAY1225 for obesity or T2D, while in the USA and/or Europe NNC0519-0130 is under development. The other combination includes the dual GCGR and GLP-1 receptor agonists AZD9550, AZD9550, mazdutide (IBI362, LY3305677) [25], maridebart cafraglutide (AMG 133), and survodutide (BI 456906) [26] for obesity or overweight treatment with or without T2D. In a Phase 2 trial, survodutide demonstrated a dose-dependent effect on body weight reduction, ranging from −6.2% to −14.9%, in patients suffering from obesity without T2D. Adverse effects (AEs) occurred in 91% patients on survodutide, and most were primarily gastrointestinal (GIT) (75%) [64]. The triple combination of receptor agonism is retatrutide as a triple GIP, GLP-1, and GCGR agonist for which Eli Lilly has big expectations [65]. In a Phase 2 trial in overweight patients with or obesity, retatrutide also demonstrated a dose-dependent effect (ranging from −8.7% to −24.2%) on body weight reduction, as well as dose related AEs, mostly GIT AEs with mild to moderate severity [28]. Another combination is cagrilintide as a new long-acting amylin analog, combined with GLP-1 RA semaglutide 2.4 mg once weekly (CagriSema) in patients with obesity or T2D. In the Phase 2 trial, in patients with T2D, the combination showed a more pronounced effect on body weight reduction than cagrilintide or semaglutide alone [29]. NNC0165-1875 as the Y2R agonist is a new approach that has yet to be proven in regard to efficacy and safety.

Non-entero-pancreatic hormone-based pharmacotherapy offers new therapeutic approaches as denatonium acetate a TAS2R agonist and ALN-KHK as siRNA conjugated with GalNAc targeting KHK. The GalNAc delivery system increased the surge of siRNA and ASO therapies, mostly in dyslipidemia or elevated Lp(a) treatment. Bimagrumab is a mAb inhibitor of ActRII, which demonstrated in a Phase 2 trial in patients with a T2D fat mass (FM) a reduction of −20.5%, body mass −6.5%, and lean mass (LM) gain 3.6% [34]. Other mAbs include the trevogrumab α-myostatin (GFD8) and garetosmab Act-A mAbs combination, and it would be interesting to see if they provide a similar beneficial effect on weight loss and LM gain. GDF-15 induces weight loss through a reduction in food intake through actions in the CNS [66]. MBL949 is under development as a GDF15 agonist. CGT therapy with rilparencel (Renal Autologous Cell Therapy-REACT®) in patients with T2D and moderate to severe CKD is novel and in early development. The first interim results of the REGEN-006 trial are expected in late 2024 [40]. A Phase 2 trial of rilparencel administered as bilateral percutaneous kidney injections into the kidney cortex demonstrated less decline in eGFR compared to the standard care group, while post-hoc analysis indicated a kidney function stabilization in patients with Stage 4 CKD and a severe urine albumin-to-creatinine ratio (UACR) [67,68]

For dyslipidemia treatment, novel PCSK9 inhibitors are in the pipeline: AZD0780 and MK-0616 as oral (daily administration) and AZD8233 and lerodalcibep as SC (monthly administration) PCSK9 inhibitors. In China, JS002 and recaticimab as mAbs against PCSK9 are under development. A new era of elevated Lp(a) and dyslipidemia treatment is occurring with ASO and siRNAs, covalently linked with GalNAc and targeting the mRNA that encodes apo(a). Olezarsen and pelacarsen are an ASO while lepodisiran olpasiran, plozasiran, solbinsiran, zerlasiran, and zodasiran are siRNAs, and muvalaplin is an orally administered small molecule inhibitor of Lp(a). Results in earlier phases (Phase 1 and Phase 2) in dyslipidemia and/or elevated Lp(a) with or without ASCVD with these new therapies are very encouraging and will probably be a new standard of care as an add-on therapy or monotherapy for these indications [42–48,69].

CEPT inhibitors have been evaluated in several RCTs, but without the expected benefit [11,12]. However, NST-1024 (SEFA-1024) and obicetrapib are a new hope for CETP inhibitors in hypertriglyceridemia and dyslipidemia treatment. In a Phase 2 trial, obicetrapib in combination with ezetimibe significantly lowered LDL-C (63.4%) in patients with dyslipidemia and high-intensity statin therapy [49]. Pemafibrate is a novel SPPARM

that has the potential to demonstrate positive results outside Japan, where it is approved for the treatment of hyperlipidemia. Compared to other PPARα agonists, pemafibrate does not significantly increase alanine aminotransferase (ALT) or γ-glutamyltransferase (GGT), and it is also excreted via the liver [50].

Baxdrostat and lorundrostat aldosterone synthase inhibitors have proved efficacy in Phase 2 trials for resistant and uncontrolled hypertension, respectively [51,53]. ION904 as an ASO conjugated with GalNAc inhibits AGT mRNA. In a Phase 2 trial in patients with uncontrolled hypertension, ION904 significantly reduced plasma AGT levels and blood pressure [54]. Zilebesiran as an siRNA conjugated with GalNAc and targeting AGT also demonstrated a significant systolic blood pressure reduction in patients with uncontrolled hypertension [56]. XXB750, a fully humanized mAb NPR1 agonist, reduced blood pressure in a dose-dependent manner in a Phase 1 trial [58].

Metabolic syndrome has no approved drugs for itself. It would be interesting to see if 6-BT may prove beneficial as an endogenous plasma microbiome-derived tryptophan metabolite or vericiguat as a stimulator of soluble guanylyl cyclase. INV-202, as a peripherally acting CB1r blocker, has shown promising results on weight loss and biomarkers in metabolic syndrome patients in a Phase 1b trial [60]. TLC-3595 as an ACC2 inhibitor has for now no published results in patients with insulin resistance.

5. Conclusions

Metabolic syndrome prevalence is between 24 and 27% and poses a significant risk for the development of ASCVD, T2D, or other various comorbidities. Currently, no drugs are approved for metabolic syndrome treatment itself, so the risk factors are treated with therapies approved for cardiac and metabolic conditions. There are many new pharmacological approaches and drug classes that have reached Phase 2 and Phase 3 RCT for the management of each of the risk factors of metabolic syndrome. GIP, GLP-1, GCGR, and amylin agonists, as well as their combinations, are under development in T2D and overweight or obesity. Non-entero-pancreatic hormone-based therapies have created several new pathways to act as a KHK inhibitor, GDF15 agonist, and mAbs as an ActRII inhibitor and to target GFD8 and Act-A. For dyslipidemia treatment, in addition to the novel PCSK9 inhibitors (oral and SC) and CETP inhibitors, a new generation of ASO and siRNAs targeting the Lp(a) synthesis pathway is on the way. For resistant and uncontrolled hypertension, aldosterone synthase inhibitors and siRNAs targeting AGT are promising new therapeutic options. It will be interesting to see whether metabolic syndrome will finally gain the first drug approval for metabolic syndrome itself.

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