White Paper

# A Renaissance for Cardiometabolic Innovation

## *Why innovators should take heart from recent advances seen in obesity and beyond*

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# Introduction

Excitement for novel obesity treatments is reaching fever pitch among industry observers and celebrities alike, even spilling over to the 2023 Oscars and causing temporary drug shortages.[1,2] This represents new territory in more than one way, as cardiometabolic innovation is taking centre-stage after having fallen out of favour with pharmaceutical companies for many years.

To understand how we got here, it is worth taking a step back and look at a brief history of cardiometabolic innovation.

The modern pharmaceutical industry was profoundly shaped by therapies for cardiometabolic diseases. In April 1981, the FDA approved Capoten, the first angiotensin converting enzyme (ACE) inhibitor for the treatment of hypertension; in October 1982 it approved Humulin, the first biosynthetic human insulin for the treatment of diabetes, while September 1987 saw the approval of the first statin, Mevacor, for treating dyslipidaemia. This signalled the start of a prolific period of cardiometabolic innovation.

High prevalence of the targeted cardiometabolic diseases combined with unmet need provided the runway for a tremendously successful business model which gave rise to many blockbuster brands, most notably statin Lipitor which generated annual peak sales of over $12 billion and held the record for the biggest selling pharmaceutical product for many years.

Such multi-billion dollar revenue streams sustained double-digit growth for the industry over several decades and led to the emergence of global, research-based pharmaceutical companies.

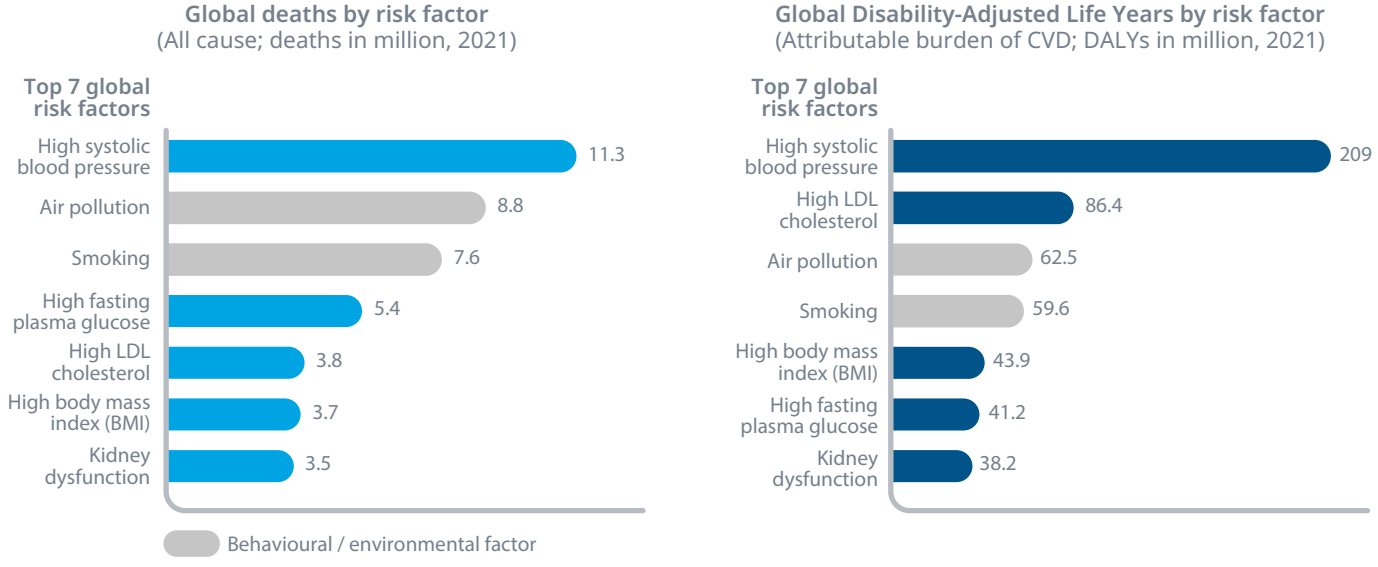
However, this golden era of innovation in cardiometabolic therapeutics came to an end when former blockbusters faced loss of exclusivity and industry focus shifted towards specialty care from the mid-2000s onwards, in particular oncology and immunology, which promised exceptional returns. This coincided with declining cardiovascular mortality rates in the developed world[3] as a result of this first wave of therapies, alongside public health interventions such as reduction in smoking, while cardiometabolic innovation pursued at the time delivered diminishing incremental benefits.

Nevertheless, significant unmet need continues to exist, with metabolic risk factors still among the leading drivers of both global mortality and the global burden of disease (see Figure 1).

Our understanding of those diseases, risk factors and the underlying biology has matured, including interdependencies between different conditions, previously neglected cardiometabolic diseases and identifying and defining new 'silent' conditions such as NAFLD and NASH as causes of high morbidity. This has opened the door for new drug targets and novel mechanisms of action to set the stage for a cardiometabolic renaissance. Moreover, impressive patient outcomes demonstrated by some new therapies have caught the attention of health systems as options for effectively managing population health.

***Metabolic risk factors are still among the leading drivers of global mortality and the global burden of disease.***

**Figure 1: Metabolic risk factors are key drivers of mortality and morbidity**




Source: Vaduganathan M, Mensah G, Turco J, et al.,The Global Burden of Cardiovascular Diseases and Risk; J Am Coll Cardiol., Dec. 2022.

# The cardiometabolic opportunity: Unmet need remains high

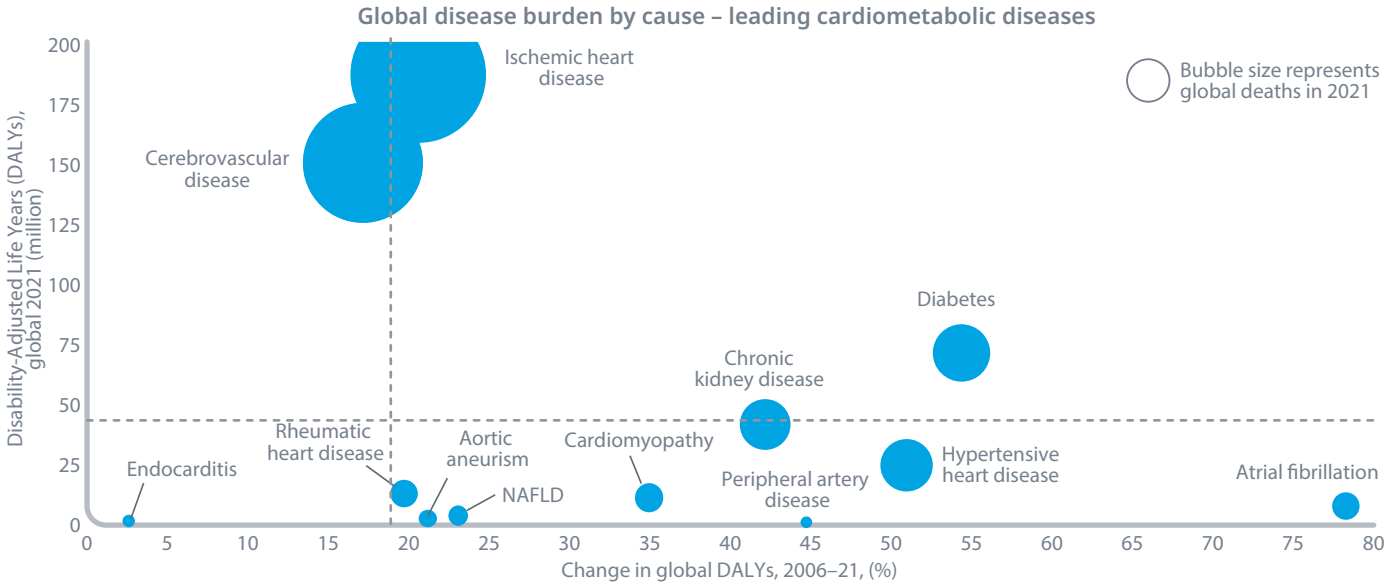
Despite significant advances in pharmacological and non-pharmacological interventions, cardiometabolic diseases remain among the leading causes of mortality and morbidity globally. In 2019, they collectively accounted for 34% of all global deaths and impacted health-related quality of life by an estimated 500 million disability-adjusted life years (DALYs) globally, an increase of 18% since 2006.[4,5] For comparison, this is double the share of global deaths caused by all malignant neoplasms and more than double their global burden of disease, estimated at 242 million DALYs in 2019.

Ischemic heart disease and cerebrovascular disease as the first and second leading cause were responsible for over 16 million global deaths alone. They also have a huge impact on people's quality of life with an estimated 334 million DALYs globally in 2021, while atrial fibrillation, diabetes, hypertensive heart disease and chronic kidney disease have seen the biggest increases in global disease burden, ranging from 42% to 78% growth in the respective number of global DALYs since 2006[5-7] (see Figure 2).

Importantly, the burden of disease is not limited to the traditional, high prevalence cardiometabolic conditions. Patients suffering from debilitating, rare cardiometabolic diseases, such as amyloidosis, pulmonary arterial hypertension (PAH) or myocarditis, often have few effective treatment options available to them. Other conditions inflict a great health burden on patients in low- and middle-income countries (LMICs), e.g., Chagas disease, particularly prevalent in Latin America and caused by parasite Trypanosoma cruzi, which leads to serious long-term heart problems, including arrhythmia and heart failure.

This high and growing burden of cardiometabolic diseases presents a major public health challenge with vast economic impact, running into the trillions of dollars. It therefore makes the effective management of underlying metabolic risk factors (see Figure 1) a meaningful target for future therapeutic innovation, especially where historically pharmacological interventions have proved difficult, and often public health interventions too, e.g., in obesity, treatment-resistant dyslipidaemia or hypertension, and in rare cardiometabolic diseases.

**Figure 2: The global burden of cardiometabolic diseases is high and growing fast**




Source: WHO, Global Health Observatory; Vaduganathan M, Mensah G, Turco J, et al., The Global Burden of Cardiovascular Diseases and Risk; J Am Coll Cardiol., Dec. 2022; IQVIA EMEA Thought Leadership analysis.

However, despite significant unmet need, cardiometabolic innovation has faced a number of obstacles[8]:

- Following loss of exclusivity of former blockbuster brands, many major cardiometabolic indications have seen a high share of generics volume utilisation, e.g., just under 80% in hypertension and dyslipidaemia, based on IQVIA MIDAS. This limits the first-line opportunity for innovators and sets low reference price points. The first oral renin inhibitor Rasilez, which represented a novel MoA for treating hypertension, is a case in point. In a highly genericised environment, Rasilez was unsuccessful in establishing a meaningful position in the market, and it failed commercially.

- Faced with demands to fund specialty care innovation when healthcare budgets are constrained, many payers have adopted a 'good enough' mindset which de-prioritises cardiometabolic innovation and implies limited perceived unmet need in such diseases.

- Cardiometabolic pipeline assets saw lower average composite success rates from phase I to regulatory filing over the past 5 years, at 6.1% vs. 8% across all TAs, and 7.6% and 15.3% for the industry's innovation hotspots of oncology and immunology, respectively.[9] This is likely a reflection of the fact that low hanging fruit was already harvested during the early heyday of cardiometabolic innovation.

- Regulators, payers and HCPs demand data from cardiometabolic outcomes trials that clearly demonstrate clinical benefits. Such outcomes trials require large sample sizes to be adequately powered and are run for extended periods of time, given typical effect sizes and the natural history of many cardiometabolic diseases, to ensure the accumulation of sufficient endpoints.

  For example, the EMPA-REG OUTCOME trial assessing the effect of Jardiance (empagliflozin) on risk of 3-point MACE, CV and all-cause death, and hospitalisation for heart failure in T2D recruited 7,020 patients[10], while the overall GALAXY programme of trials investigating the impact of Crestor (rosuvastatin) on CV risk reduction and patient outcomes enrolled an astonishing 69,000 patients from 55 countries worldwide.[11] This in turn translates into higher clinical development cost, especially compared to the much smaller, often single-arm trials relying on surrogate endpoints used in oncology.

***Despite significant unmet need, cardiometabolic innovation has faced a number of obstacles.***

- Innovation may disrupt established clinical practices, patient experiences and care pathways for treating cardiometabolic diseases, such as introducing a biologic therapy into an indication with an oral standard of care or crossing different settings of care involving referrals from GPs to specialists, e.g., for diagnosis or to administer a novel treatment at a hospital.

These challenges are real, as illustrated by the struggle to date of the PCSK9 inhibitors to gain traction in the dyslipidaemia market.

At the same time, numerous recent examples of commercially successful cardiometabolic innovation prove that those challenges can be overcome, e.g., Entresto in heart failure, the indication expansion of SGLT-2 inhibitors from diabetes into heart failure and chronic kidney disease, the forays of GLP-1 receptor agonists liraglutide and especially semaglutide from diabetes into obesity, or Onpattro, the first small interfering RNA (siRNA) therapeutic approved for the treatment of hereditary transthyretin-mediated amyloidosis (hATTR).

Innovators should therefore take heart from these success stories while heeding important lessons from new therapies that entered the cardiometabolic market.

# The cardiometabolic pipeline and innovation highlights

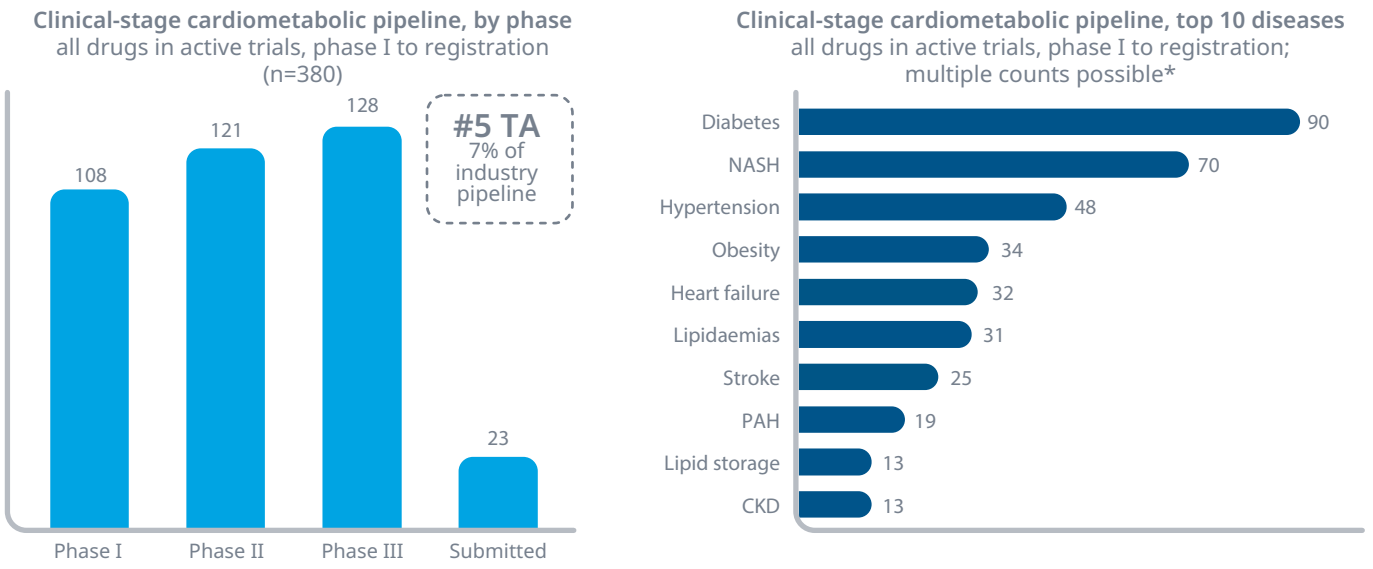
Over the past 5 years, the number of clinical-stage cardiometabolic assets has increased by 13% and now accounts for 7% of the overall industry R&D pipeline[9], which puts this group of diseases at fifth place in the ranking of therapy areas by pipeline size.

The top 5 diseases in focus of cardiometabolic development are diabetes, NASH, hypertension, obesity and heart failure, which collectively represent about 50% of the clinical-stage cardiometabolic pipeline (see Figure 3). Many assets are being investigated across multiple cardiometabolic conditions, a reflection of the improved understanding of the underlying biology, natural history and mechanistic interdependencies of different diseases.

Select pipeline highlights showcase the cutting edge of cardiometabolic innovation which seeks to address remaining high unmet need in many conditions, for example:

- **Dyslipidaemia**: Oral PCSK9 inhibitor MK-0616[12] is aiming to combine efficacy with patient convenience vs. injectable incumbents; lipoprotein(a) is evolving from a biomarker of atherosclerotic cardiovascular disease (ASCVD) to a target in its own right for novel therapies, e.g., siRNA olpasiran[13] or antisense drug pelacarsen.[14]
- **Hypertension**: New therapeutic modalities are being investigated for controlling blood pressure in patients with treatment-resistant hypertension, e.g., dual endothelin antagonist aprocitentan, selective aldosterone synthase inhibitor baxdrostat, or third-generation non-steroidal mineralocorticoid receptor antagonist ocedurenone for uncontrolled hypertension in advanced chronic kidney disease (CKD) patients.[15]
- **Diabetes**: Immunotherapy approaches[16] are being explored to delay the onset of T1D, e.g., anti-CD3 antibody teplizumab, recently approved as Tzield[17]; or even bolder moves, e.g., Vertex VX-264, a cell therapy to restore islet cell function in T1D.[18] In T2D, several small molecule GLP-1 receptor agonists, e.g., orforglipron or RGT-075, are aiming to offer alternative oral options to Rybelsus[19]; new dual action approaches such as GLP-1R/GIP (Mounjaro)[20] or GLP-1R/amylin (CagriSema)[21] are pushing the boundaries of HbA1c reduction while delivering significant, beneficial weight loss at the same time.

**Figure 3: Cardiometabolic represents ~7% of the total industry pipeline**




* Cardiometabolic assets are often investigated in multiple diseases, eg diabetes, obesity, heart failure, NASH, CKD
Source: IQVIA EMEA Thought Leadership; IQVIA Pipeline Link May 2023.

- **Obesity**: GLP-1 receptor agonist Wegovy was approved as an effective anti-obesity therapy delivering 15% weight loss[22], while multiple, promising new assets are in development, with tirzepatide the most advanced.[23] Truly transformative, early approaches are exploring durable and disease-modifying therapies, e.g., Resalis Therapeutics investigating non-coding RNA-based therapeutics in obesity and other metabolic disorders.[24]

  Given the extraordinary recent breakthroughs in obesity, we will further elaborate in more detail on key trends that are transforming the obesity market in the deep dive section below.

- **NASH:** Following a period of setbacks, several assets have emerged as potential treatment options for NASH, e.g., selective thyroid hormone receptor-β agonist resmetirom, which delivered impressive phase III data in late 2022[25]; or mid-stage FGF21 analogues pegozafermin and efruxifermin, or selective thyroid receptor-beta agonist VK2809 following closely behind with equally promising phase IIb data, while several key mid- and late stage readouts are expected throughout 2023 and 2024, including GLP-1 receptor agonists.[26,27]

- **Rare cardiometabolic diseases**: Second generation gene silencers, e.g., vutrisiran or eplontersen, are being investigated for treating transthyretin amyloid cardiomyopathy (ATTR-CM), a progressively debilitating, rare disease associated with high mortality.[28] Other early studies are exploring in vivo gene editing approaches using CRISPR-Cas9 to produce a durable knockout of TTR in patients with the same disease.[29]

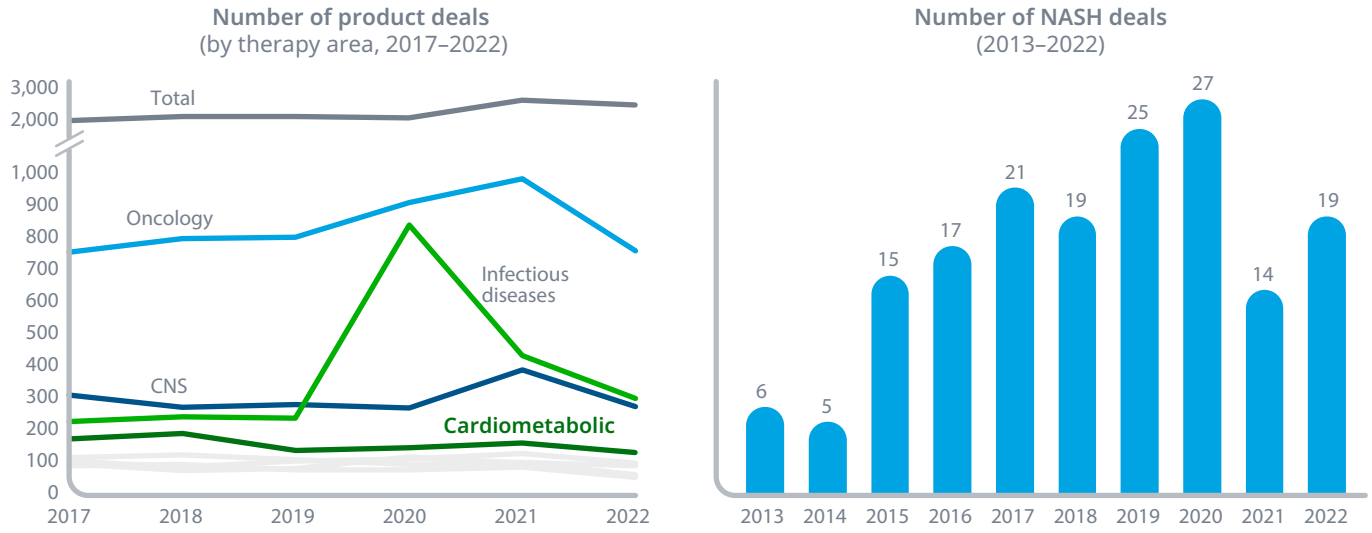
  In pulmonary arterial hypertension (PAH), activin signalling regulator sotatercept is set to become the first disease-modifying therapy following impressive phase III readout[30], with several other candidates targeting the underlying causes of PAH in development, e.g., seralutinib, inhibitor of PDGFR α/β, colony stimulating factor 1 receptor and stem cell factor receptor[31]; bromodomain inhibitor apabetalone[32], or Aurora-GT, a gene therapy targeting endothelial nitric oxide synthase to rebuild blood vessels in the lung.[33]

These examples clearly illustrate that today's cardiometabolic innovation has come a long way since the early days when many of those conditions were treated with therapies which formed the bedrock of traditional primary care. The emerging, future cardiometabolic therapies are anything but, drawing on a wide range of the latest technology platforms, including mRNA.[34] Remarkably, 26% of the clinical-stage pipeline of advanced therapy medicinal products (ATMPs), including cell, gene and RNA therapeutics, is focused on cardiometabolic diseases, making it the second largest therapy area in focus after oncology.[35]

Over the past 5 years, cardiometabolic assets accounted for an average of 7% of all product-focused transactions, as larger players looked to external sources of innovation. This puts cardiometabolic in fourth place in the therapy area ranking by deal volume, behind oncology, infectious diseases and CNS. Interest in NASH assets has increased considerably, which is also consistent with NASH accounting for the second largest number of clinical-stage assets in the industry's cardiometabolic pipeline. Over the

*Cardiometabolic innovation has come a long way and draws on a wide range of the latest technology platforms, including cell, gene and RNA therapeutics.*

**Figure 4: Cardiometabolic deal-making trends**




Source: IQVIA Pharma Deals; IQVIA EMEA Thought Leadership analysis.

past 5 years, we saw an average of 21 NASH-focused transactions p.a., a fourfold increase from deal activity levels ten years ago (see Figure 4).[36]

Notable cardiometabolic deal examples include the $11.5 billion acquisition of Acceleron by Merck, which centred on sotatercept for PAH[37]; the $1.8 billion acquisition of CinCor by AstraZeneca, giving the latter access to lead asset baxdrostat for treatment resistant hypertension[38]; the partnership deal between Novo Nordisk and Aspect Biosystems to develop cell-based therapies for diabetes and obesity, which could be worth $2.6 billion, including milestone payments[39]; or the licensing agreement between Vertex and CRISPR Therapeutics, worth $330 million, to develop hypoimmune cell therapies for T1D.[40]

*Cardiometabolic assets represent ~7% of all product-focused transactions, making it the fourth largest TA by deal volume.*

## Deep Dive: The obesity market at an inflection point

Obesity is a major global health crisis impacting every corner of the world, with some of the most rapid increases in prevalence seen in low- and middle-income countries.

The global prevalence of obesity, defined as having a body mass index (BMI) equal to or greater than 30 kg/m$^2$, is expected to rise from 14% of the world's population in 2020 to 24% by 2035, or 1.9 billion people. When the overweight population is included, i.e. those having a BMI equal to or greater than 25 kg/m$^2$ but less than 30 kg/m$^2$, prevalence more than doubles to 4 billion.[41] This dramatic trend has a huge economic impact, estimated at $4 trillion in 2035 or 2.9% of global GDP, as a result of higher healthcare cost and lost economic productivity.[42]

Unsurprisingly, weight loss medications have captured innovators' attention as potential solutions, however, the obesity market has a history of many false dawns, as drugs in the past failed to deliver meaningful efficacy while some had serious safety issues, e.g., Fen-Phen, which was eventually withdrawn from the market due to cardiac risks.[43]

The arrival of the GLP-1 receptor agonists, especially Wegovy, marked an inflection point for the obesity market, because for the first time pharmacological interventions delivered meaningful weight loss of 10–15%. Given the huge scale of unmet need, the market for anti-obesity drugs is expected to grow rapidly and reach $30–50 billion by 2030[44], while the most bullish analysts even predict that a staggering $100+ billion global obesity market will ultimately emerge.[45]

*The arrival of the GLP-1 receptor agonists marked an inflection point for the obesity market.*

The ability of new obesity treatments to demonstrate, via cardiovascular outcomes trials (CVOT), that weight loss translates into a significant reduction in major adverse cardiovascular events (MACE) will be a critical catalyst for unlocking the obesity opportunity, which makes the readout of the Wegovy SELECT outcomes trial in mid-2023 a watershed moment.[46]

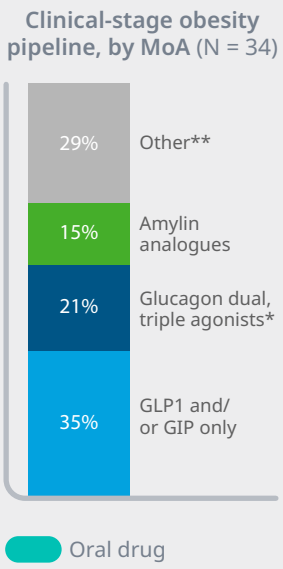
Leading diabetes players Novo Nordisk and Lilly are set to dominate the race for the obesity opportunity. However, its future trajectory is far from linear as many uncertainties remain, e.g., acceptance of obesity as a chronic disease, budget impact faced by payers and health systems' willingness and ability to pay, the readout of CVOTs, or new entrants challenging first generation therapies with alternative mechanisms of action (MoA) to address shortcomings such as gastrointestinal tolerability, current drugs being injectables, or the durability and quality of weight loss which distinguishes between fat and lean body mass.

### INNOVATION LANDSCAPE

The current obesity pipeline comprises 34 clinical-stage assets that are being investigated in trials specifically for this condition, as opposed to treating obesity as a co-morbidity of diabetes. It is dominated by GLP-1 receptor agonists which on their own or in combination with GIP agonists account for 35% of candidates. Glucagon/GLP-1R dual agonists and glucagon/GLP-1R/GIP triple agonists hold a combined share of 21% of the obesity pipeline, while amylin analogues represent 15%. The remainder of 29% comprises a range of different mechanisms of action, e.g., SGLT2, MGAT2, MC4R, PDE5, PYY and insulin receptor modulator. Ten of those clinical-stage assets, or 29%, are oral therapies, seeking to offer effective weight loss combined with greater convenience (see Figure 5).

## Figure 5: The clinical-stage obesity pipeline

| PHASE I | | PHASE II | | PHASE III | |
|---|---|---|---|---|---|
| DACRA QW II (Lilly) | HM15211 (Hanmi) | Coladutide (AstraZeneca) | MBL949 (Novartis) | CargiSema (Novo) | Tirzepatide (Lilly) |
| VK2735 (Viking) | HM15136 (Hanmi) | PF-07081532 (Pfizer) | Noiiglutide(Jiangsu Hengrui) | Semaglutide (Novo) | |
| Amycretin (Novo) | DWP306001 (Daewoong) | Danuglipron (Pfizer) | BI 456906 (Boehringer/Zealand) | | |
| Sco-094 (Scohia Pharma) | S-309309 (Shionogi) | NN9775 (Novo) | NS-0300 (Nusirt) | | |
| Sco-267 (Scohia Pharma) | AMG-786 (Amgen) | Orforglipron (Lilly) | AMG-133 (Amgen) | | |
| ZP6590 (Zealand) | LY3841136 (Lilly) | Retatrutide (Lilly) | Pemvidutide (Altimmune) | | |
| ZP8396 (Zealand) | AZD6234 (AstraZeneca) | Tesomet (Saniona) | Mazdutide (Innovent) | | |
| Dapiglutide (Zealand) | CN4211 (Cohbar) | | | | |
| LB54640 (LG Chem) | | | | | |
| 17 | | 14 | | 3 | |

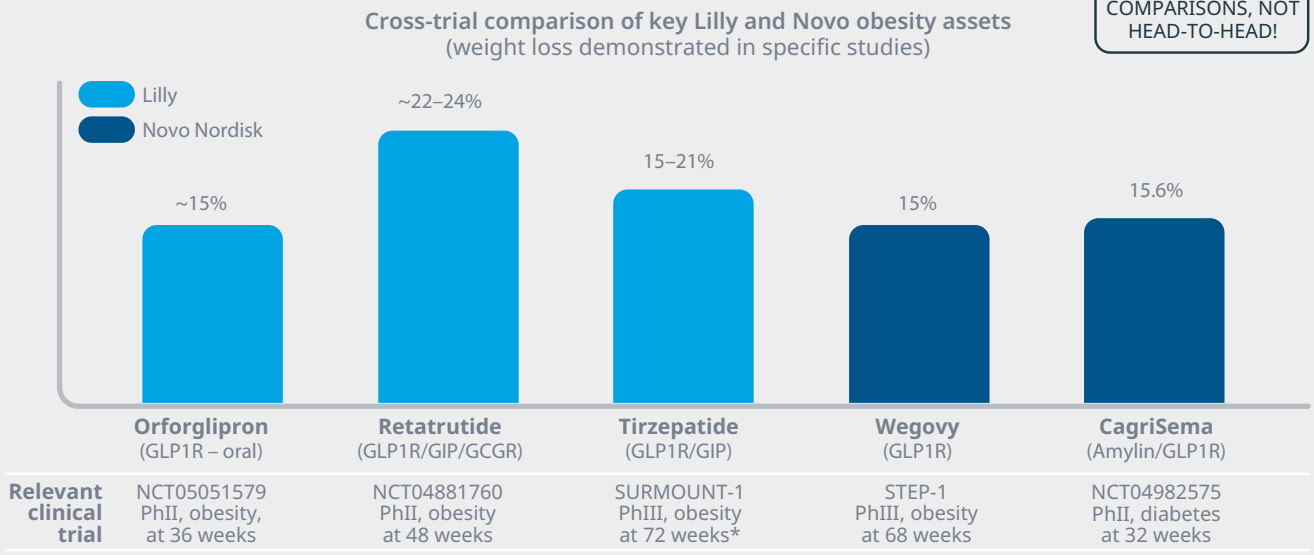



* Includes dual and triple agonists targeting glucagon and GLP1R/GIP; ** Includes SGLT2, MGAT2, MC4R, PYY, PDE5, Insulin receptor modulator, activin type II, other
Source: IQVIA Pipeline Link, May 2023; IQVIA EMEA Thought Leadership analysis.

Novo Nordisk and Lilly are setting a high benchmark for weight loss with their novel obesity treatments, including approved Wegovy and other assets currently in development. Dual- and triple action approaches which simultaneously target multiple pathways, for example, GLP1R/GIP (tirzepatide), GLP1R/GIP/glucagon (retatrutide) or amylin/GLP1R (CagriSema) appear more potent and may push weight reduction to the mid-20% range and possibly beyond, while oral options seek to deliver levels of efficacy seen with injectables (see Figure 6).

## Figure 6: Novel obesity treatments are setting a high efficacy bar

**CAVEAT:** CROSS-TRIAL COMPARISONS, NOT HEAD-TO-HEAD!




| | Orforglipron (GLP1R – oral) | Retatrutide (GLP1R/GIP/GCGR) | Tirzepatide (GLP1R/GIP) | Wegovy (GLP1R) | CagriSema (Amylin/GLP1R) |
|---|---|---|---|---|---|
| **Relevant clinical trial** | NCT05051579 PhII, obesity, at 36 weeks | NCT04881760 PhII, obesity at 48 weeks | SURMOUNT-1 PhIII, obesity at 72 weeks* | STEP-1 PhIII, obesity at 68 weeks | NCT04982575 PhII, diabetes at 32 weeks |

* Efficacy expressed as treatment-regimen estimands; Notes: GCGR – glucagon receptor agonist
Source: Clinicaltrials.gov; company presentations, trial results announcements; NEJM; J Investig Med; product label; IQVIA EMEA Thought Leadership analysis.

As competition is heating up, ultimately head-to-head trials will be needed to demonstrate unambiguous differentiation, which Lilly has just embarked on with its bold SURMOUNT-5 obesity trial which pits its tirzepatide against Novo's Wegovy.[47]

At the same time, compelling cardiovascular outcomes data will be equally critical for commercial success to demonstrate value to health systems:

- **Novo's SELECT** trial investigates the impact of Wegovy-induced weight loss on the risk of having cardiovascular events in overweight or obese patients with prior cardiovascular disease. Its primary outcomes measure is time to first occurrence of a composite endpoint consisting of cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke; while a range of secondary measures assess impact on co-morbidities such as heart failure, hypertension, dyslipidaemia, hyperglycaemia, renal disease.[48] It will be the first CVOT to read out, expected in mid-2023, and signify a defining moment.

*The readout of the Wegovy SELECT CV outcomes trial will be a watershed moment.*

- **Lilly** is recruiting for its **SURMOUNT-MMO** trial to investigate the effect of tirzepatide on the reduction of morbidity and mortality in obese adults. Its primary outcomes measure is time to first occurrence of any component event of a composite endpoint comprising all-cause death, non-fatal myocardial infarction, non-fatal stroke, coronary revascularization, or heart failure events that result in hospitalization or urgent hospital visits. Secondary endpoints assess impact on multiple co-morbidities, e.g., MACE-3 events, onset of T2D, hypertension, heart failure or renal disease. Trial completion is estimated for Q4/2027.[49]
- **Lilly's** ongoing **SURPASS-CVOT**, while focused on cardiovascular outcomes in T2D patients and comparing Mounjaro (i.e. tirzepatide) vs. Trulicity, is expected to read out in Q4/2024, before SURMOUNT-MMO, and thus could provide important, earlier outcomes data in support of tirzepatide even for its obesity indication.[50]

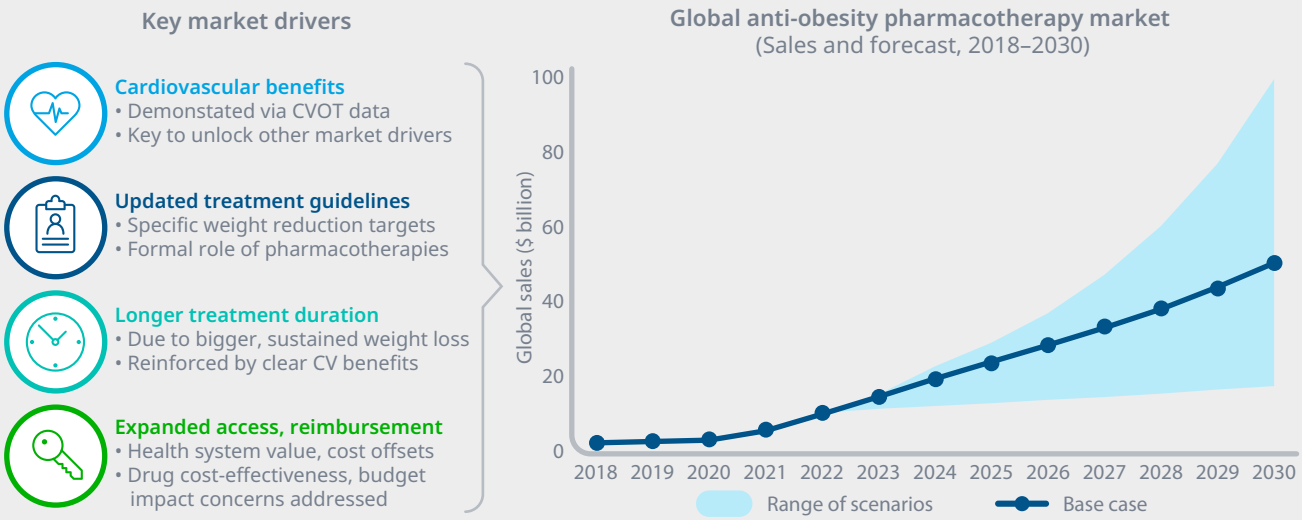
Future competitors will have to clear a high bar to challenge today's leading two players, possibly delivering weight reduction of 20% or more while demonstrating beneficial cardiovascular outcomes. Recent phase II trial readouts from Boehringer Ingelheim/Zealand and Innovent illustrate the battle ahead. Their respective glucagon/GLP-1R dual agonist assets, BI 456906 and mazdutide, delivered weight loss of ~15%, which puts them in the efficacy range of Wegovy, but trailing the 21% weight reduction seen with tirzepatide in a cross-trial comparison, with its inherent caveats.[51,52]

However, successful challengers will also look beyond headline efficacy numbers to other differentiators, such as tolerability, the quality of weight loss and its durability.

For example, overweight and obese T2D patients treated with activin type 2 receptor antagonist bimagrumab in a phase II trial achieved net weight loss, comprising significant loss of total body fat mass while gaining some lean mass (i.e. muscle), in addition to seeing improvements in glycaemic control.[53] Furthermore, earlier trials of bimagrumab showed that weight and fat loss were maintained for 12 weeks after patients stopped treatment.

Other approaches are looking to trigger secretion of a range of appetite- and glucose-regulating hormones, e.g., GLP-1, GLP-2, glicentin, PYY or CCK, at naturally occurring levels, with the aim to achieve weight loss with better tolerability of treatments.[54,55]

**Figure 7: The global obesity market is at the cusp of a major expansion**




Source: IQVIA Forecast Link, May2023; IQVIA EMEA Thought Leadership analysis.

Beyond biopharma innovators, other types of players, such as telehealth and digital health companies, have also been attracted by the obesity opportunity, for example, offering prescription services for anti-obesity drugs as part of comprehensive weight loss or disease management programmes for chronic conditions, which typically include counselling on behavioural, nutrition and activity changes with the aim to achieve lasting weight reduction.[56]

## THE FUTURE OBESITY MARKET: KEY DRIVERS

Recent innovation trends have undoubtedly signalled a step-change in the treatment paradigm for obesity by introducing highly effective pharmacotherapy options. However, despite increasing prevalence and high unmet need, the extent of their commercial success and the wider outlook for the obesity market are still fraught with uncertainty.

A significant expansion of the market for anti-obesity pharmacotherapies from its current, nascent state to reach a size of potentially many tens of billions of dollars depends on a number of critical drivers (see Figure 7):

- **Compelling CVOT data**: Ultimately, health systems attribute value to cardiovascular outcomes, not weight loss on its own. Therefore, the readout of Novo's SELECT cardiovascular outcomes trial represents a moment of truth for the future trajectory of the obesity market, with profound ramifications beyond Wegovy itself. Compelling outcomes data that demonstrate the value of weight management will be critical for any expansion of access and reimbursement and change in clinical practice.

  In a scenario in which Wegovy demonstrates compelling cardiovascular outcomes, Lilly and other followers are still likely to be expected to generate evidence to support cardiovascular benefits of their own obesity treatments. In the long run, real world studies will become essential to substantiate benefits, including weight loss and CV outcomes, achieved in an everyday life setting.

- **Treatment guideline updates**: A change in clinical practice is an important driver for market expansion. In the U.S., for example, only 2% of the obese adult population were historically treated with anti-obesity drugs, due to a combination of lack of clarity about the role and value of pharmacotherapies, limited insurance coverage and resulting out-of-pocket costs.[57]

  Updated treatment guidelines for obesity which specify weight management targets for obese patients, with or without T2D, are needed to codify positive CVOT data and embed their implications in clinical practice for optimal CV risk reduction. This in turn would formalise the role of pharmacotherapies in the treatment of obesity and, in combination with educational efforts, would improve diagnosis and treatment rates from historical lows.

- **Longer treatment duration**: Several real-world studies assessing the use of Saxenda for weight management found patients' typical persistence with therapy lasts for around 5–7 months.[58-60] Compared to Saxenda, patients in clinical trials receiving next generation treatments Wegovy or tirzepatide achieved more than three times the weight reduction, or ~15–20% vs. ~5%. Furthermore, under clinical trial conditions Wegovy and tirzepatide continued to deliver significant, incremental weight loss until week 48, and even beyond for higher doses.[61,62] It is therefore plausible to expect that patients will remain on therapy for much longer with these new, potent anti-obesity treatments as they continue to see weight loss benefits, while positive cardiovascular outcomes data would further strengthen this case. Even so, such optimistic assumptions are yet to face their real world test.

- **Access and reimbursement expansion**: Historically, coverage of weight loss medications by both private and public payers has often been highly restricted, and in many countries such treatments are not reimbursed at all, reinforcing health inequities.[63] The arrival of next generation therapies which deliver meaningful weight reductions has reignited the debate about expanding reimbursement and access to such treatments.

  In the U.S., the yet to be passed Treat and Reduce Obesity Act of 2021 seeks to lift the statutes prohibiting Medicare coverage of obesity drugs.[64] However, the substantial budget impact of covering obesity treatments is a major concern, which given the size of the potential target patient population could even exhaust the entire Part D budget under certain scenarios.[65] Meanwhile, commercial payers are divided on the value of obesity medicines and coverage has shown wide variations.

  Outside the U.S., some countries are expanding access to new anti-obesity therapies, e.g., the UK and France[66,67], but tight restrictions apply.

  For example, the UK's NICE[68] recommends Wegovy for weight management alongside diet and exercise, but it is restricted to (i) patients with at least one weight-related comorbidity, and (ii) a BMI of at least 35.0 kg/m$^2$; while (iii) reimbursement is limited to a maximum of two years, and (iv) the drug must be used within a specialist weight management service providing a multidisciplinary approach. Only by exception, patients with a BMI of 30.0 kg/m$^2$ to 34.9 kg/m$^2$ may be considered if they meet additional guideline criteria.

  To truly unlock wide access to novel obesity treatments, positive cardiovascular outcomes data will be absolutely critical to demonstrate substantial cost-savings for health systems from medication-assisted weight loss by avoiding downstream complications from obesity-related comorbidities. In addition to outcomes data, payers will be guided by cost-effectiveness considerations, e.g., as assessed by European HTA bodies or ICER, with implications for drug prices to meet acceptable cost-effectiveness thresholds.

Notwithstanding the buzz surrounding the novel weight loss treatments, which is vividly playing out on social media and beyond, capturing this commercial opportunity will still require an orderly, rigorous approach to create and shape a new market. For example, medical-led engagement of HCPs, professional societies and guideline setting bodies will be critical to educate, disseminate compelling evidence and facilitate the adoption of new clinical practice. The same applies to payers and policy makers, to help elevate obesity as a public health priority that deserves attention and adequate funding.

For all the exuberance about the tremendous potential of the obesity market, the fate of the PCSK9 inhibitors may serve as a cautionary tale. Despite their potent efficacy and clear superiority over the standard of care, they faced many challenges, e.g., concerns about budget impact due to high price and target population size, lack of CV outcomes data at launch, questions about their cost-effectiveness and, as injectables, they disrupted entrenched clinical practice. In the end, the PCSK9 inhibitors never came close to analysts' initial, sky-high expectations of a $40+ billion market for this class.

Undeniably, this is an exciting time for the obesity market as it is facing a major inflection point. Over the next 18–24 months we will find out whether the stars are indeed aligning to unlock what could be one of the most significant commercial opportunities the pharmaceutical industry has seen in decades.

# Outlook for the cardiometabolic market

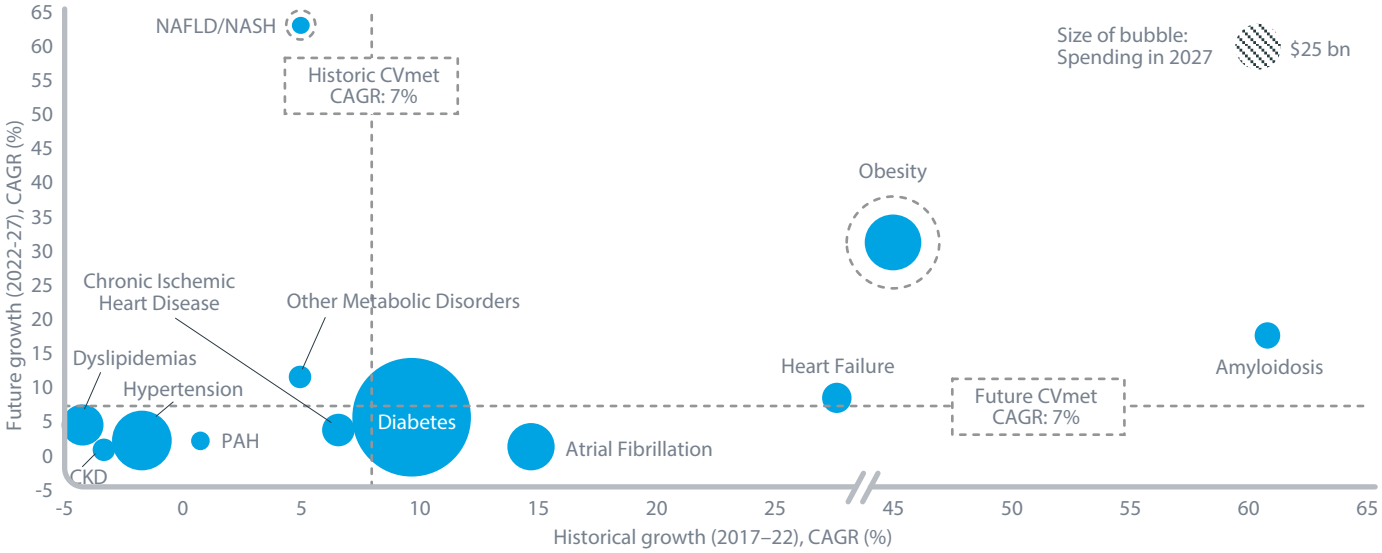
The umbrella of cardiometabolic diseases collectively represents a sizeable, global market worth $264 billion in 2022, at ex-manufacturer prices. We expect growth to continue over the next 5 years at the historical 5-year CAGR (2017-2022) of 7%, with the combined cardiometabolic market set to reach $370 billion globally by 2027.

However, this aggregated perspective masks a more differentiated picture in which pockets of high growth co-exist with segments weighed down by high levels of generics utilisation that also suppress overall headline growth rates. Furthermore, the cardiometabolic market comprises a diverse set of diseases with different trends in prevalence, levels of unmet need and availability of effective treatment options, which translates into a wide range of disease-specific growth trajectories (see Figure 8).

For example, the arrival of the first disease-modifying treatments in NASH has the potential to trigger rapid growth but depends on non-invasive diagnostic techniques becoming more mature, e.g., blood biomarkers or imaging biomarkers; the new generation of highly effective anti-obesity treatments will establish a new standard of care and sustain future double-digit growth rates for this market, while in dyslipidaemia, innovative therapies, such as antisense drugs, are poised to reverse a historical decline driven by 79% volume share of generics into positive, mid-single digit overall growth.

This latter example illustrates the coexistence of market segments with starkly different growth dynamics within a disease and the importance for innovators to look beyond headline growth figures when appraising opportunities.

**Figure 8: Wide range of growth trajectories reflects diversity of cardiometabolic**



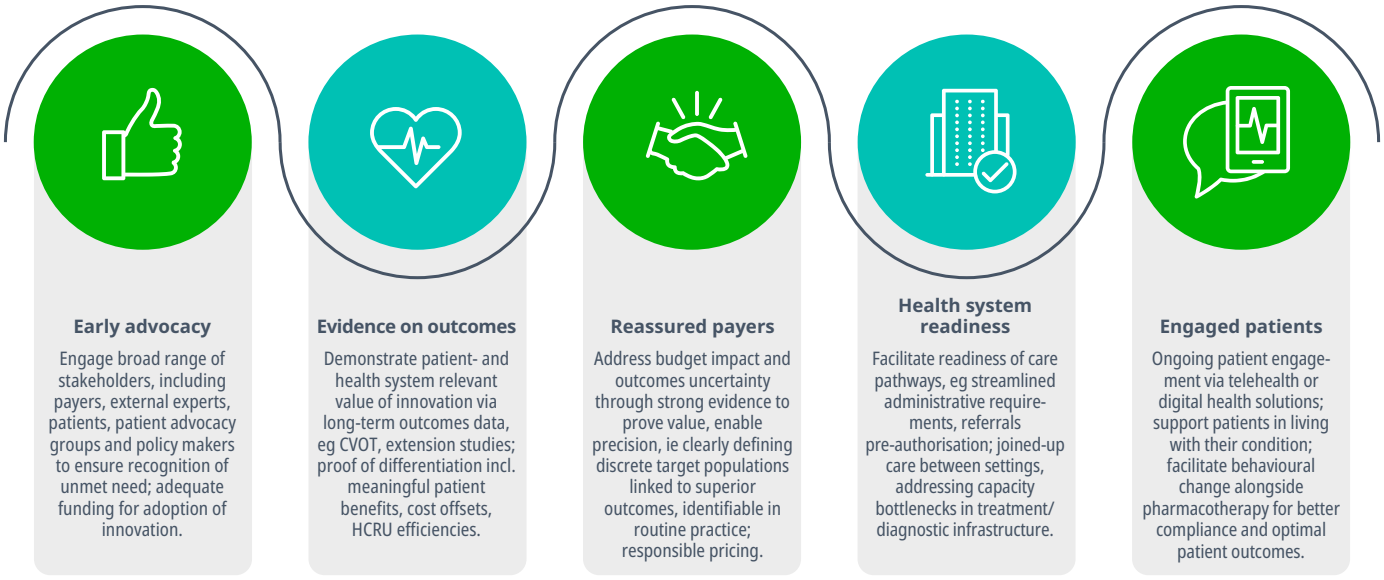

Source: IQVIA Forecast Link, IQVIA MIDAS Dec 2022, IQVIA Institute report: The Global Use of Medicines 2023; IQVIA EMEA Thought Leadership analysis.

# Succeeding with cardiometabolic innovation

Cardiometabolic innovation undeniably spans a wide spectrum of therapeutic modalities and technology platforms which are applied across a diverse set of diseases. Nevertheless, we have identified five common, critical priorities cardiometabolic innovators must address to achieve commercial success (see Figure 9):

- **Early advocacy**: Cardiometabolic innovators face two challenging scenarios: (i) Where an entrenched legacy standard of care exists, innovators often face an uphill struggle against a 'good enough' mindset which doesn't recognise unmet need; (ii) Conversely, in conditions without any existing treatment options, lack of awareness is a typical barrier to overcome when innovators must create a new market. In either scenario early engagement of a broad range of stakeholders, including payers, external experts, patients, patient advocacy groups and policy makers is essential to build advocacy and unlock the commercial opportunity. Policy makers are particularly important stakeholders for recognising and elevating cardiometabolic diseases as a public health priority to secure adequate and sustainable funding for the adoption of innovation.
- **Evidence on outcomes**: Demonstrating value that is both patient- and health system relevant is critical for cardiometabolic innovation to succeed. This will require generating long-term outcomes data, e.g., via cardiovascular outcomes trials, or extension studies for long-term follow-up under real-world conditions, which demonstrate differentiation including meaningful patient benefits, cost offsets for payers or efficiencies in healthcare resource utilization (HCRU). To effectively address the collective needs of all key stakeholders, innovators need to develop an integrated evidence strategy, starting early, which combines clinical trial data, RWE as well as patient-generated data, e.g., via connected, digital devices.
- **Reassured payers**: Payers want to de-risk two types of uncertainty they face. To address budget impact uncertainty, given the potential size of target populations, and outcomes uncertainty, e.g. in heterogeneous populations different from those in clinical trials, cardiometabolic innovators will need strong evidence to prove value and to enable precision, i.e. clearly defining discrete target populations linked to superior outcomes which are identifiable in routine clinical practice. Furthermore, innovators must ensure transparency of responsible

**Figure 9: Succeeding with cardiometabolic innovation**




Source: IQVIA EMEA Thought Leadership.

pricing which reflects both differential value and patient volume. Notwithstanding their limited success to date, there is still a worthwhile case to be made for exploring alternative access models, such as outcomes-based or population-level agreements.

- **Health system readiness**: Most cardiometabolic diseases have traditionally been treated in a GP-centric setting, however, delivery of novel innovative therapies may cross different settings of care, involving multiple prescriber specialties and may also introduce different forms of administration, such as injectables or infusions. To enable the optimal adoption of their novel therapies, innovators must engage health systems to facilitate readiness of care pathways, e.g. streamlined administrative requirements such as referrals or pre-authorisation, joined-up care between settings, and addressing capacity bottlenecks in treatment delivery infrastructure. Diagnostic readiness is equally important to enable therapy adoption, especially for 'silent', asymptomatic conditions such as NASH or in rare cardiometabolic diseases which lack established, validated diagnostic techniques or are not routinely tested.
- **Engaged patients**: Many cardiometabolic diseases are chronic conditions where underlying physiological disorders intersect with patient behaviours. Therefore, to achieve optimal patient outcomes, ongoing engagement is important, e.g., via telehealth or digital health solutions, to support patients in dealing with the practicalities of day-to-day living with the condition and to facilitate behavioural change, including improved compliance, alongside pharmacotherapeutic interventions. Furthermore, capturing longitudinal digital measures including vital signs, patient behaviours, activities and relevant health outcomes, could form the basis of tailored patient support programmes and allow HCPs, via a closed feedback loop, to optimise individual disease management plans.

With the exception of rare cardiometabolic diseases, scale will likely give innovators a competitive advantage, because engagement of GPs is an important part of the go-to-market model for high prevalence conditions. They play a key role in cardiometabolic patient journeys and relevant care pathways typically start at the GP. However, this does not mean a return to the old, share of voice driven primary care model requiring massive commercial infrastructure. Instead, a new primary care model is needed, which for example is more targeted and utilises omnichannel approaches. Even so, adequate customer engagement inevitably will require critical scale.

As the leading causes of mortality and morbidity globally, today and for the foreseeable future, cardiometabolic diseases are an indisputable public health priority and thus a worthwhile focus for innovators. Recent therapeutic breakthroughs and early commercial successes seen in obesity, and beyond, should encourage biopharmaceutical companies to become part of this renaissance for cardiometabolic innovation.

*Recent therapeutic breakthroughs and early commercial successes seen in obesity, and beyond, should encourage biopharmaceutical companies to become part of this renaissance for cardiometabolic innovation.*

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