

White Paper

Targeting Residual Risk: The Next Wave of Cardiovascular, Renal and Metabolic Innovation

Beyond obesity, a strategic outlook on the CVRM pipeline, market and routes to commercial success

MARKUS GORES, Vice President, Thought Leadership, IQVIA

STEFAN LUTZMAYER, Senior Consultant, Thought Leadership, IQVIA

SOPHIE MARLOW, Summer Intern, Thought Leadership, IQVIA



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Introduction

Since the publication of our white paper 'A renaissance for cardiometabolic innovation' in 2023, the biopharmaceutical industry's renewed interest in an area it had largely neglected for much of the previous two decades has yielded some remarkable breakthroughs.¹

Incretin-based pharmacotherapies have truly transformed weight management, unleashed extraordinary consumer demand and propelled obesity up the ranks to become the fourth largest therapy area by value, generating \$66Bn in global sales in 2025, at ex-manufacturer prices.

Meanwhile, Madrigal made history in March 2024 when the FDA approved its oral, thyroid hormone receptor beta agonist Rezdiffra as the first therapy for metabolic dysfunction-associated steatohepatitis (MASH), which had become a notorious graveyard for drug development.

In May 2026, AstraZeneca's Baxfendy was approved for the treatment of hypertension, introducing the first aldosterone synthase inhibitor to this market and bringing hope to the many patients inadequately served by existing therapy options.

These examples clearly illustrate that innovation focused on cardiovascular-renal-metabolic (CVRM) diseases is alive and well and delivers transformational benefits for patients.

But there is more to do. CVRM risk factors continue to be among the leading drivers of both global mortality and the burden of disease and thus represent key targets for effectively managing population health.

In this white paper, we will explore the latest trends in CVRM innovation, including a deep dive into selected therapeutic breakthroughs, and provide an outlook on the competitive landscape and the CVRM market opportunity.

Since obesity, understandably, is often the centre of attention and extensively covered in many reviews, we will focus in this white paper on ex-obesity CVRM innovation, while acknowledging the interdependencies with obesity therapies as they impact a range of CVRM risk factors beyond BMI.



The CVRM opportunity: Unmet need, and complexity, continue to rise

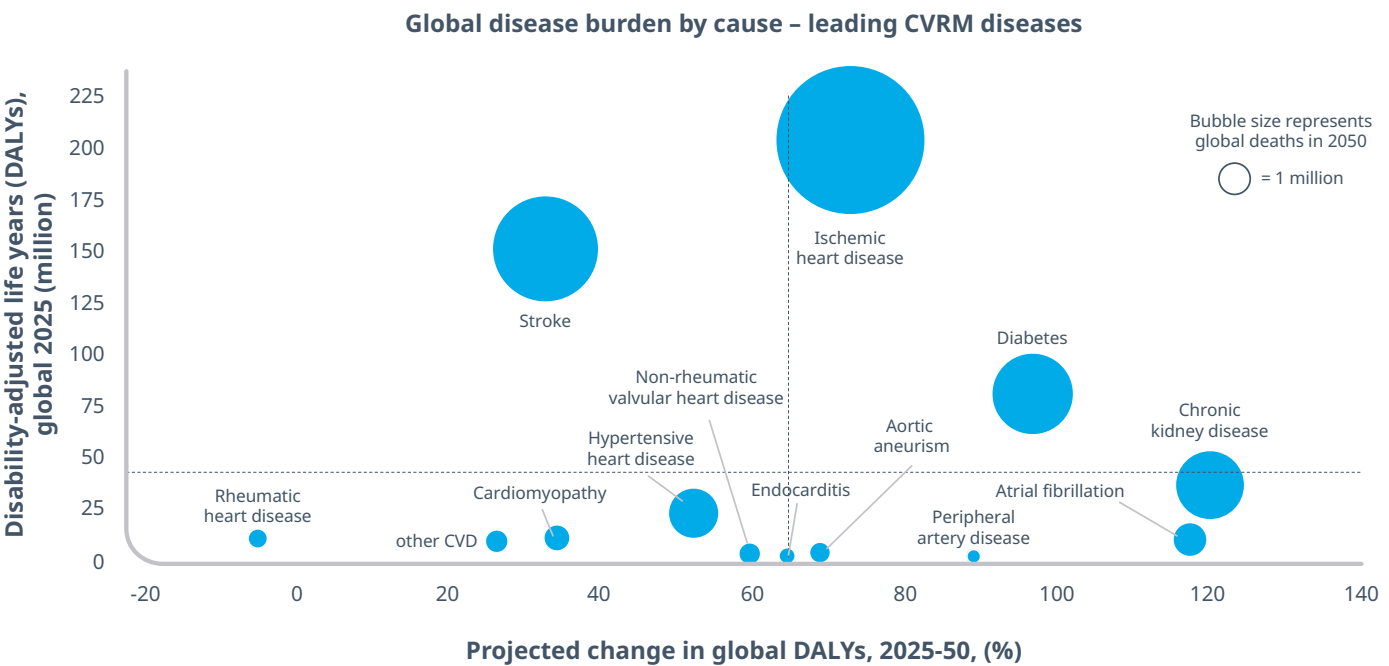
Cardiovascular-renal-metabolic diseases contributed to over 25 million deaths in 2025. While advances in public health measures and pharmacotherapeutic interventions are reducing age-standardized mortality, a growing and ageing, global population more than offsets such gains, with CVRM-related deaths forecast to increase sharply by 80% and exceed 45 million globally by 2050,^{2,3} For comparison, global deaths caused by all malignant neoplasms are expected to reach 18 million in 2050.⁴

CVRM diseases also have a huge impact on people’s quality of life with an estimated 545 million DALYs globally in 2025, which is projected to rise to 900 million by 2050, an increase of 65%. Again, this surpasses the estimated 388 million DALYs attributed to all malignant neoplasms in 2050.^{2,3}

Ischemic heart disease and stroke, as the first and second leading cause of mortality and morbidity, were responsible for over 17 million global deaths alone in 2025 and together impacted health-related quality of life by an estimated 355 million DALYs.³

Meanwhile chronic kidney disease, atrial fibrillation, diabetes and peripheral artery disease are forecast to see the biggest increases in global disease burden by 2050, ranging from 89% to 120% growth in respective global DALYs (see Figure 1).

Figure 1: The global burden of CVRM diseases is high and growing fast



Source: Global burden of CVDs: projections from 2025 to 2050, European Journal of Preventive Cardiology, 2025; Burden of disease scenarios for 204 countries and territories, 2022-2050, Lancet 2024

This significant and rapidly growing burden of CVRM diseases poses a major public health challenge with vast economic impact, running into the trillions of dollars. Targeting the underlying risk factors with pharmacotherapeutic interventions therefore presents an attractive opportunity for innovators.

The unique complexity of the CVRM opportunity

One of the defining features of CVRM diseases is the substantial overlap between different patient populations, because many indications manifest themselves as co-morbidities in the same patient (see Figure 2).

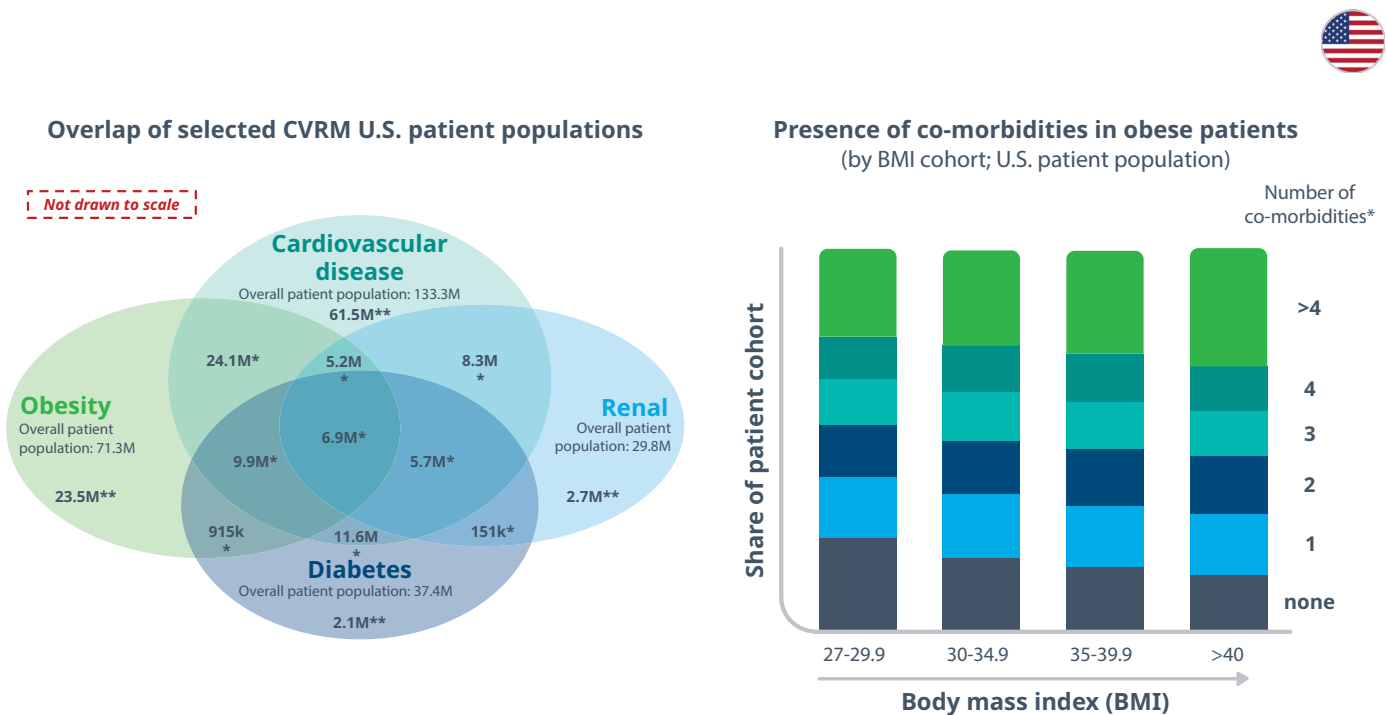
As we discussed elsewhere⁵ such interdependencies between different indications create strategic and operational complexity for CVRM innovators, e.g., defining the target product profile and the ideal patient benefiting the most from a new treatment, conducting clinical trials in highly co-morbid patient populations who are likely on multiple background therapies, or segmenting patients in routine practice and identifying those eligible for a specific therapy.

One of the defining features of CVRM diseases is the substantial overlap between different patient populations, because many indications manifest themselves as co-morbidities in the same patient

Another recent complication is the arrival of incretin-based obesity treatments that have demonstrated benefits against multiple CVRM risk factors, beyond BMI. They are thereby blurring the boundaries between indications and also move the goal posts of what constitutes residual unmet need that an innovator may seek to address.

Incretin-targeting therapeutics now join SGLT2 inhibitors as ‘backbone agents’ that deliver broad benefits across the CVRM disease spectrum: directly, as treatments with multi-indication labels; and indirectly, by lowering risk factors related to indications for which they are not approved, as a secondary benefit of treating in-label indications.

Figure 2: Substantial overlap between different CVRM populations



*Represents number of patients in each Venn diagram overlap; **Represents number of patients in a single TA, i.e. have no comorbidity overlap
Patient population sizes include 2022+ data-active patients, or those with Rx or Dx claims in 2022 or 2023;
Not shown due to diagram spacing: Obesity and Renal ONLY overlap; Obesity, Diabetes, and Renal ONLY overlap
Source: IQVIA LAAD, January 2018 to June 2023

As such, these backbone agents transform the management of CVRM diseases by re-setting the overall risk baseline across the indication spectrum, while residual risk may be addressed by layering specific disease targeting therapies on top (see Figure 3).

Backbone agents transform the management of CVRM diseases by re-setting the overall risk baseline across the indication spectrum

At the same time, this model raises an important question about the large group of established CVRM therapies that sit between backbone agents and treatments targeting residual risk. These include generic antihypertensives, lipid-lowering drugs and heart-failure therapies. Rather than being displaced, many of these treatments are likely to maintain or even increase their use in the near term, supported by broader treatment guidelines, tighter LDL-C and blood-pressure targets, and better diagnosis in primary care. Their share of market value may continue to decline, but they will remain a central part of routine CVRM care.

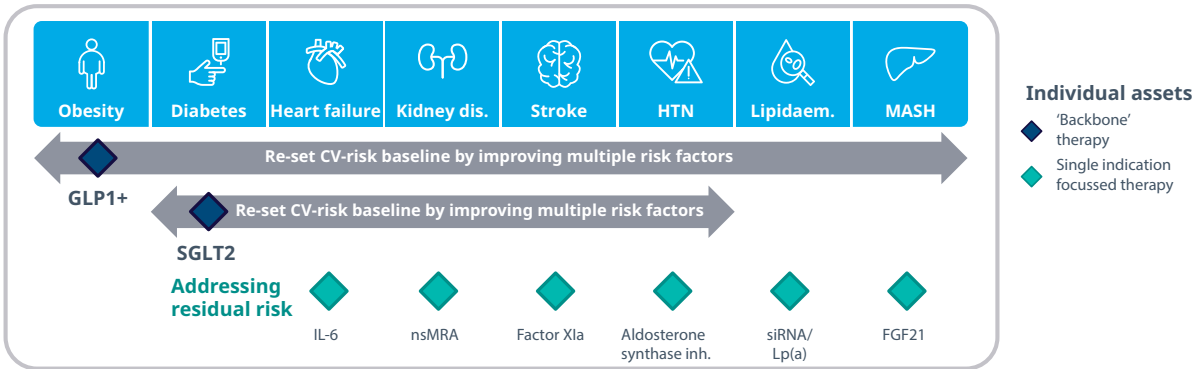
For innovators, this cuts both ways. Low-cost generics with decades of outcomes evidence set a high bar for new entrants. At the same time, the guideline changes that sustain their use also support earlier and more intensive treatment, creating more opportunities to add new therapies for patients whose risk remains inadequately controlled.

Taken together, the interplay between backbone agents, established standard-of-care therapies and treatments targeting residual risk has profound implications for CVRM innovators.

Firstly, they need to understand exactly how this upstream-downstream interplay shapes the therapeutic opportunity they are pursuing, and what this means for defining target patient profiles. And secondly, it elevates the importance of exploring combination approaches, with implications for an innovator’s overall CVRM portfolio strategy.

Recent success stories provide clear proof that the CVRM opportunity is real and compelling. However, innovators must be prepared to master the unique complexity inextricably linked to the CVRM disease space.

Figure 3: Backbone therapies are transforming CVRM risk management



Inter-dependencies

- Backbone therapies re-define, possibly shrink downstream opportunities in residual risk
- A winning CVRM strategy: from single asset to combination/portfolio play

HTN: hypertension; IL-6: interleukin-6 inhibitor; nsMRA: non-steroidal mineralocorticoid receptor antagonist; ASI: aldosterone synthase inhibitor; siRNA: small interfering RNA; LP(a): lipoprotein (a); FGF21: fibroblast growth factor 21

Source: IQVIA Thought Leadership

The CVRM pipeline and innovation highlights

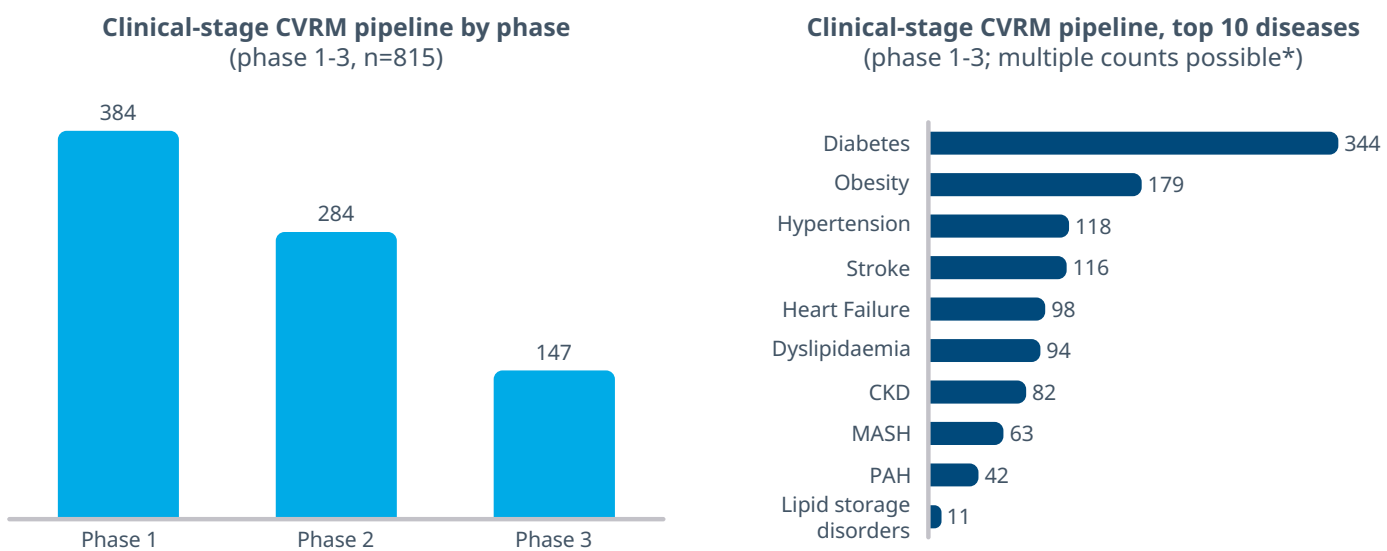
The renewed momentum behind CVRM innovation is reflected in the growing scale of clinical development. CVRM trial starts increased from 759 in 2015 to 1,063 in 2025, when they accounted for 18% of all global trial starts. Obesity has been a key driver of growth in recent years, while cardiovascular and diabetes trials together represented around half of CVRM activity. At the same time, clinical development success rates have improved markedly, particularly in cardiovascular and metabolic/endocrinology programmes.⁶

This momentum is also evident in the clinical-stage pipeline, which comprises 815 Phase 1–3 assets across a broad range of CVRM diseases (Figure 4).⁷ The strong weighting towards early-stage assets reflects continued appetite for new innovation and novel approaches across CVRM, with developers pursuing a broad range of modalities and therapeutic strategies. Diabetes and obesity account for the largest numbers

of assets, but activity extends across hypertension, stroke, heart failure, dyslipidaemia, MASH, chronic kidney disease and pulmonary arterial hypertension. Many of these assets are being investigated across multiple indications. This cross-indication development reflects the shared biology and overlapping patient populations discussed earlier, as well as the growing role of therapies that can influence several components of CVRM risk.

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Figure 4: CVRM clinical-stage pipeline



*CVRM assets are often investigated in multiple diseases, e.g., diabetes, obesity, heart failure, NASH, CKD
Source: IQVIA Thought Leadership; Global Data, accessed July 2026; secondary research

Select pipeline highlights illustrate four important shifts in the innovation frontier:

- **Greater biological precision:** New approaches seek to address risk that persists despite established backbone therapies. Examples include Lp(a), APOC3 and ANGPTL3 in dyslipidaemia, and aldosterone synthase and hepatic angiotensinogen in hypertension; and APOL1 inhibition in genetically defined kidney disease. Combination approaches are also beginning to connect broad metabolic risk reduction with targeted control of residual risk. Regeneron has announced plans for a clinical programme combining olatorepatide, a dual GLP-1/GIP receptor agonist, with Praluent, its anti PCSK9 monoclonal antibody.⁸ Inflammation remains a potential residual-risk pathway, with IL-6 and NLRP3 among the targets under investigation. However, the Phase 3 ZEUS result provides an important caution: Novo Nordisk reported that ziltivekimab lowered free IL-6 and hsCRP but did not reduce MACE versus placebo.⁹ Likewise, Novartis' pelarcasen lowered Lp(a) levels but the trial did not meet its primary endpoint of lowering cardiovascular events.¹⁰ This illustrates the difficulty of translating residual inflammatory risk and biomarker responses into clinical benefit.
- **More convenient and durable treatment:** Oral PCSK9 inhibitors, fixed-dose combinations and long-acting RNA therapeutics seek to reduce treatment burden and improve persistence. At the cutting edge, gene-editing approaches raise the prospect of one-time intervention. However, irreversible editing faces an unusually high safety, evidence and payer bar in chronic diseases where effective, reversible alternatives already exist. The largest near-term impact may therefore come from long-acting, reversible treatments that fit existing care pathways rather than from scientific breakthroughs. In chronic and often asymptomatic conditions, convenience and durability are not merely product attributes: they may determine whether clinical efficacy translates into real-world effectiveness.
- **Earlier and potentially disease-modifying intervention:** Recent advances are moving treatment upstream from the management of established disease towards interception or modification of its underlying biology. Rezdiffra has validated THR-beta agonism in MASH, Winrevair has validated

activin-signalling inhibition in PAH and Tziend has demonstrated that immune intervention can delay the onset of clinical type 1 diabetes. Cell-replacement approaches extend this ambition towards restoring islet function. In kidney disease, APOL1 inhibition is similarly testing whether treatment can move from slowing non-specific CKD progression towards targeting a causal genetic driver.¹¹

- **Closer integration of therapeutics and diagnostics:** Many emerging CVRM targets are silent, heterogeneous or underdiagnosed. Their value will therefore depend on systematic patient identification, including Lp(a) testing, eGFR and uACR measurement for CKD, non-invasive fibrosis assessment for MASH and autoantibody screening in type 1 diabetes. hsCRP may support inflammatory-risk enrichment, but its predictive value for response to targeted anti-inflammatory treatment remains unproven. Screening, biomarker interpretation and referral pathways must therefore evolve alongside therapeutic innovation rather than being addressed only after launch.

Taken together, these developments suggest that CVRM innovation is moving beyond incremental improvements of established primary care medicines. Many programs are aiming for greater precision, longer-lasting effects or modification of the underlying disease processes. But much of the pipeline remains early stage, and promising biomarker effects have not always translated into better clinical outcomes. Therapies that change practice will need to show meaningful benefit beyond current standard of care and work within the realities of how patients are identified, treated and followed in routine practice.

This expanding innovation base is also shifting competition from individual assets towards portfolios that combine broad risk reduction with targeted treatment of residual risk, as discussed in the next section.

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The competitive landscape in CVRM

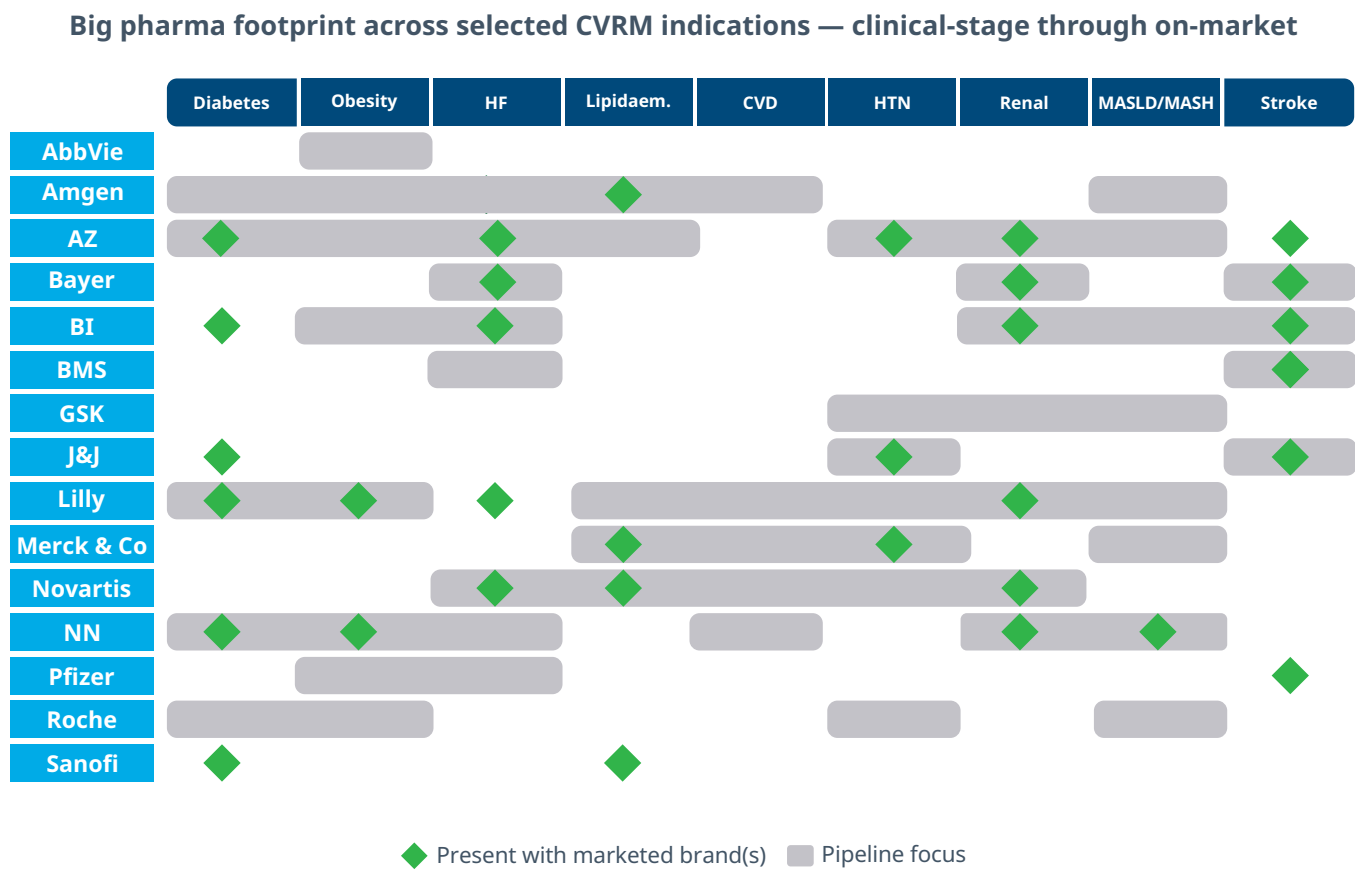
For the past decade and a half, much of the pharmaceutical industry turned its back on CVRM diseases, and primary care in general, in pursuit of opportunities in specialty care, in particular oncology. However, we are witnessing a CVRM renaissance with renewed interest from big pharma in tackling high prevalence conditions that extends beyond the hype surrounding obesity.

In fact, many of the top 15 pharmaceutical companies are establishing a broad presence across the CVRM disease spectrum, including players without a CVRM legacy placing significant bets, e.g., Roche (see Figure 5).

It is noteworthy that a CVRM strategy anchored on single asset/single indication play is the rare exception among these efforts. Instead, many companies are assembling multi-asset portfolios, including some multi-indication assets, that span a range of CVRM diseases. This reflects the distinct characteristics of CVRM, with overlapping, comorbid patient populations and the interplay between backbone agents and therapies targeting residual risk, as we discussed earlier.

Many of the top 15 pharmaceutical companies are establishing a broad presence across the CVRM disease spectrum, including players without a CVRM legacy placing significant bets

Figure 5: We are witnessing a CVRM renaissance



Source: IQVIA Thought Leadership; IQVIA Pipeline Link, June 2026; company websites; Copyright © 2026 IQVIA. All rights reserved

A closer look at the respective underlying pipeline compositions reveals four strategy archetypes across the CVRM competitive landscape (see Figure 6):

- **Ex-obesity pure play**, with companies' pipelines focusing exclusively on CVRM indications other than obesity, e.g., Novartis, Bayer, Merck, GSK and J&J.
- **Broad CVRM play**, where companies are pursuing a wide range of >10 indications, including obesity, to establish a broad CVRM presence, e.g., AstraZeneca, Boehringer Ingelheim and Lilly.
- **Focussed CVRM bet/obesity-plus**: In this strategy archetype, companies seek to establish a less expansive CVRM footprint, typically spanning 5-7 indications, by being more selective in pursuing indications beyond obesity, e.g., Amgen, Novo Nordisk and Roche.
- **Bet on obesity**, with companies' pipelines overwhelmingly, or exclusively, focused on obesity, e.g., Pfizer and AbbVie.

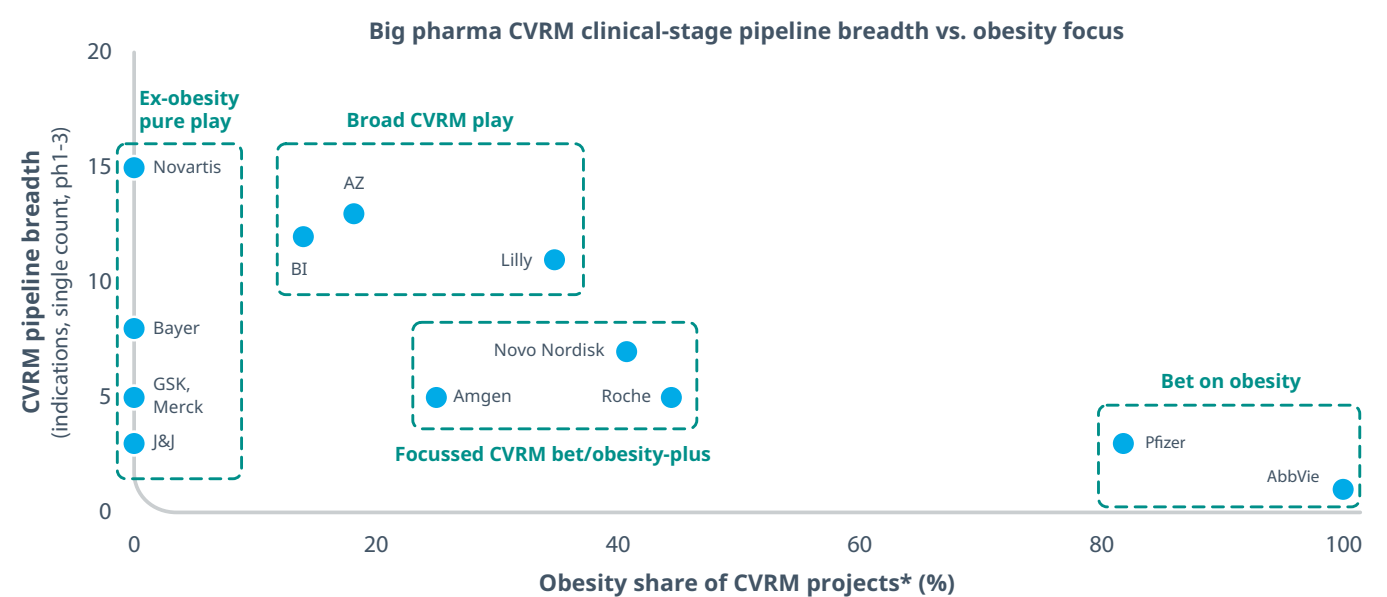
These archetypes represent different strategic portfolio choices for how companies position themselves to navigate the unique complexity of the CVRM opportunity, including the emphasis they place on obesity and optionality for combination play.

The external sourcing of innovation plays an important role as companies seek to establish, or expand, their CVRM presence. Since emerging biopharma companies (EBPs) account for 85% of clinical-stage assets in the industry CVRM pipeline, with many at the forefront of innovation, they become attractive targets for bigger players to advance their CVRM ambitions via partnering, licensing and acquisitions.

In 2025, CVRM was the #2 therapy area in focus of M&A transactions with a value share of 22%, including a high-profile bidding war as Pfizer and Novo Nordisk were vying for Metsera's portfolio of differentiated obesity assets.¹² Other CVRM M&A highlights include the respective acquisitions of MASH assets by Roche, Novo Nordisk, GSK and Madrigal, or Novartis gaining access to innovation targeting inflammation as a driver of CVRM risk.

CVRM assets were also a major focus of the surge in Chinese-to-international licensing activity as the #3 TA with a 20% share of such deals in 2025.

Figure 6: CVRM competitive landscape: strategy archetypes



Note: Lilly, Merck only disclose ph2/ph3 data; ph1-3 data used for all other companies
*Project = asset-indication combination, ph1-3; allows multiple counts of assets developed for multiple CVRM indications
Source: IQVIA Thought Leadership; IQVIA Pipeline Link, June 2026; company websites; Copyright © 2026 IQVIA. All rights reserved

Deep dive: CVRM innovation highlights

The modern cardiovascular prevention paradigm was strongly shaped by the Framingham Heart Study, which showed that cardiovascular events are closely linked to identifiable — and often modifiable — risk factors such as high blood pressure, elevated cholesterol, smoking, excess weight and physical inactivity.¹³ The following deep dives focus on dyslipidaemias and hypertension: two foundational CVRM areas where persistent gaps in risk-factor control continue to drive innovation.

I. Dyslipidaemias

INNOVATION LANDSCAPE

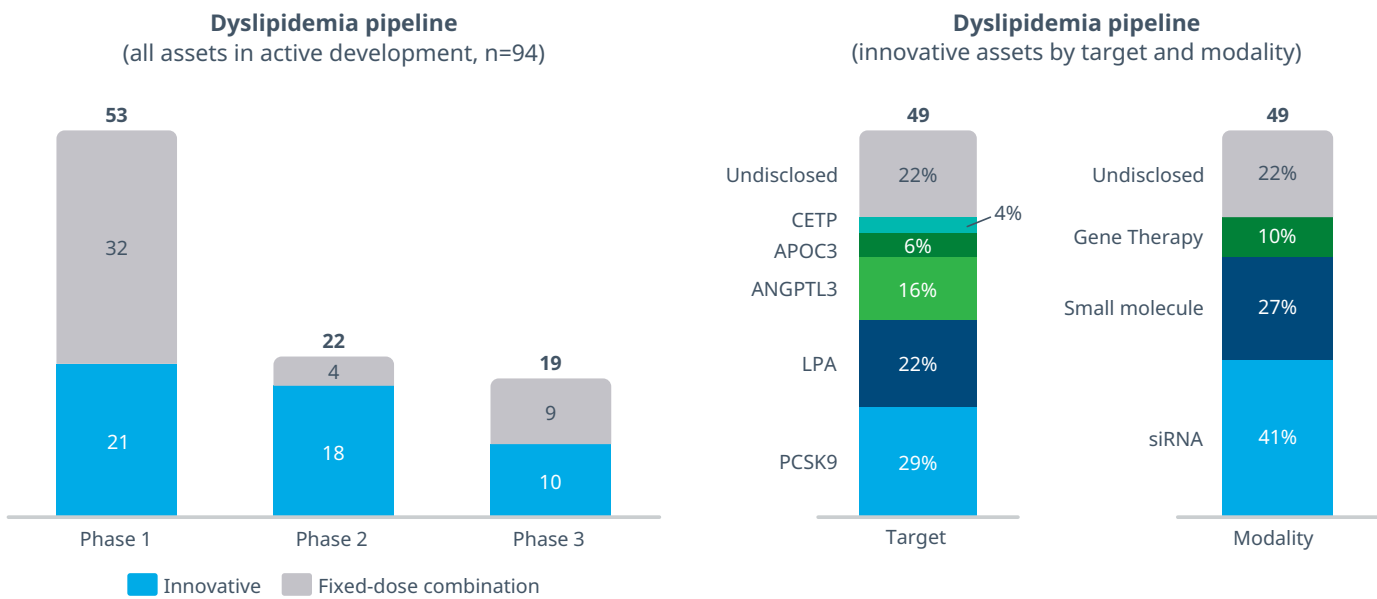
Dyslipidaemias are among the most well-established and best-understood risk factors for atherosclerotic cardiovascular disease (ASCVD). Yet, despite decades of progress, heart attacks and strokes remain the leading cause of mortality worldwide, while elevated LDL-C alone was responsible for an estimated 3.6 million deaths globally in 2023.¹⁴ Originally discovered in moulds, statins transformed cardiovascular disease prevention following their introduction in the late 1980s and have since become some of the most widely used medicines globally. Additional waves of innovation, including bempedoic acid, ezetimibe, PCSK9 inhibitors and, more recently, RNA-based approaches, have further expanded the treatment armamentarium. Nevertheless, LDL-C remains poorly controlled in routine clinical practice, with many high-risk patients failing to achieve recommended targets and only around 60% of patients demonstrating good long-term adherence to lipid-lowering therapy.^{15,16} Because patients rarely perceive an immediate benefit from lipid lowering, real-world value depends not only on efficacy but also on treatment convenience, persistence and effective communication of long-term cardiovascular risk. Important residual risk factors, such as lipoprotein(a) [Lp(a)] and triglyceride-rich lipoproteins, also remain inadequately addressed by existing therapies. These persistent gaps leave dyslipidaemia as a major contributor to cardiovascular risk despite decades of therapeutic progress, sustaining demand for both more durable treatment approaches and therapies that address residual risk.

The current pipeline reflects these dual challenges and comprises 94 clinical-stage assets, of which approximately half are fixed-dose combinations (FDCs) or reformulations built around established therapies (Figure 7, left panel). These programmes seek to reduce pill burden, improve treatment persistence and increase the likelihood that patients achieve recommended lipid targets. Among innovative programmes, activity is concentrated around a relatively small number of targets, with PCSK9, LPA, ANGPTL3 and APOC3 accounting for 29%, 22%, 16% and 6% of innovative assets, respectively (Figure 7, right panel). The modality mix points to a shift away from traditional daily oral therapies towards increasingly durable interventions, with RNA-based therapeutics accounting for 41% of innovative assets, gene therapies for a further 10% and small molecules for 27%.

Important residual risk factors, such as lipoprotein(a) [Lp(a)] and triglyceride-rich lipoproteins, also remain inadequately addressed by existing therapies.



Figure 7: Dyslipidemia clinical-stage pipeline



Source: IQVIA Thought Leadership; Global Data, accessed July 2026; secondary research

Together, these trends suggest that future innovation in dyslipidaemia will be driven by two complementary objectives: achieving more reliable LDL-C control through increasingly convenient and durable treatment approaches and addressing specific sources of residual lipid-mediated cardiovascular risk, particularly Lp(a) and triglyceride-rich lipoproteins.

Among these targets, **PCSK9** has been among the most validated pathways in lipid management. Originally identified through genetic studies of familial hypercholesterolaemia, PCSK9 regulates the availability of LDL receptors on hepatocytes and thereby plays a central role in controlling circulating LDL-C levels.¹⁷ Injectable monoclonal antibodies have established that PCSK9 inhibition can achieve profound LDL-C reductions and reduce cardiovascular risk, while inclisiran has demonstrated durable LDL-C lowering with infrequent dosing of twice per year. Uptake has nevertheless been constrained by injection burden on healthcare professionals, payer restrictions and complex treatment pathways. Recent innovation has focused on expanding access to this class of drugs through increasingly convenient treatment modalities. Merck’s Lipfendra (enlicotide) became the first oral PCSK9 inhibitor approved in the U.S., marking an important milestone for the class and potentially broadening access to

Recent innovation has focused on expanding access to this class of drugs through increasingly convenient treatment modalities

PCSK9 inhibitors.¹⁸ Follow-on oral agents, including AstraZeneca’s AZD0780, are being developed alongside RNA-based and gene-editing approaches that seek to further extend dosing intervals or potentially provide one-time treatment. For example, Verve Therapeutics’ VERVE-102, an investigational PCSK9 base-editing therapy now owned by Eli Lilly, reduced LDL-C by up to 62% following a single administration in open-label Phase Ib testing in adults with heterozygous familial hypercholesterolaemia or premature coronary artery disease who required additional LDL-C lowering.¹⁹ These reductions were achieved despite most patients already receiving intensive lipid-lowering therapy, including high-intensity statins (71%) and ezetimibe (43%). Although its current development is focused on selected patients with high lifetime cardiovascular risk, the approach is not restricted to genetically confirmed familial hypercholesterolaemia because it targets PCSK9 rather than correcting the underlying disease-causing mutation. These early results support the potential for

one-time treatment, but the development bar will be high: long-term durability, off-target editing and an acceptable risk-benefit profile must be established for a potentially permanent genomic intervention.

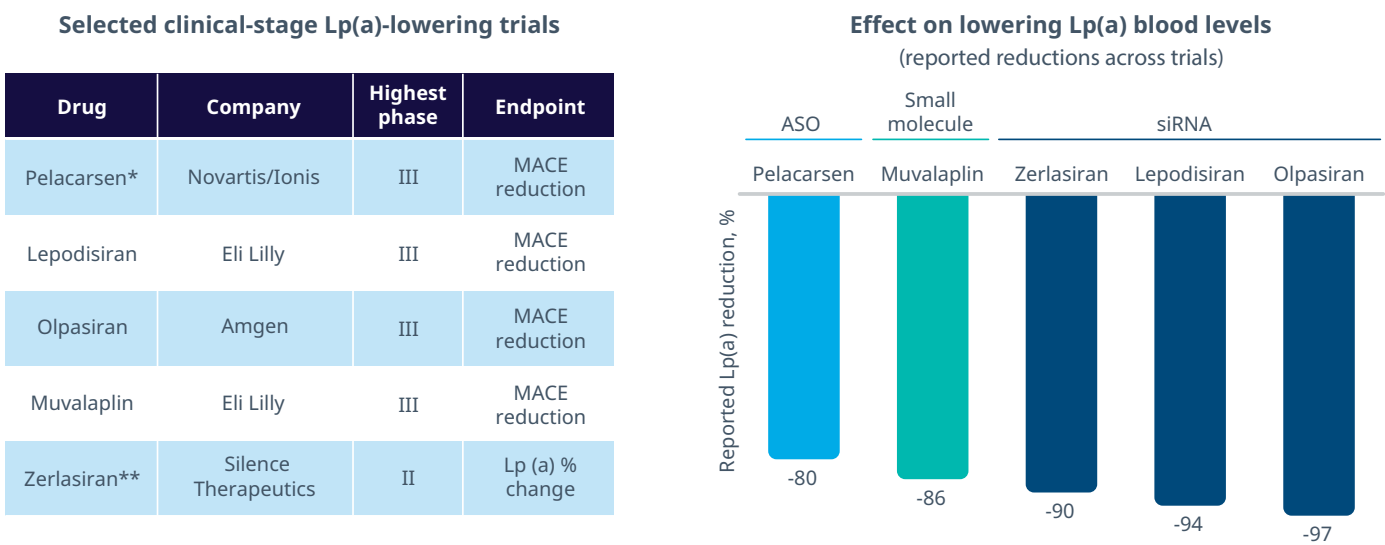
Alongside PCSK9, **CETP inhibition** has re-emerged as a potentially important oral approach to LDL-C lowering. After earlier setbacks in the class, obicetrapib has renewed interest by demonstrating substantial additional LDL-C reductions on top of existing therapies and, in July 2026, received positive CHMP opinions in Europe both as a standalone medicine and in a fixed-dose combination with ezetimibe.²⁰ Its oral profile and combination potential could position it as a scalable option for the broad population of patients who remain above target despite standard therapy, potentially bridging the gap between established oral add-on therapies and injectable PCSK9 inhibitors. Cardiovascular outcomes data from PREVAIL will nevertheless be central to determining its ultimate clinical and commercial role.²¹

While these approaches seek to make intensive LDL-C lowering more effective, convenient and accessible, a second wave of innovation is expanding the scope of lipid management beyond LDL-C. Growing evidence implicates triglyceride-rich lipoproteins and remnant cholesterol in residual cardiovascular risk, driving interest in targets such as **APOC3** and **ANGPTL3**.^{22,23} Therapies against these targets were originally developed for rare genetic disorders including familial chylomicronaemia syndrome (FCS) and homozygous familial hypercholesterolaemia (HoFH). These pathways are now being explored in broader populations with severe hypertriglyceridaemia, mixed dyslipidaemia and elevated cardiovascular risk. Recent milestones include the approval of olezarsen for severe hypertriglyceridaemia, representing the first expansion of an APOC3-targeting therapy beyond orphan disease.²⁴ Multiple pipeline programmes have demonstrated substantial reductions in triglycerides, remnant cholesterol, ApoB and non-HDL cholesterol, further supporting these pathways as therapeutic approaches to residual cardiovascular risk. Biomarker improvements alone may not be sufficient but the ability of these therapies to reduce cardiovascular events will ultimately determine their role in broader residual-risk management.

Multiple pipeline programmes have demonstrated substantial reductions in triglycerides, remnant cholesterol, ApoB and non-HDL cholesterol, further supporting these pathways as therapeutic approaches to residual cardiovascular risk

Among residual-risk targets, **Lp(a)** remains a potential category-creation opportunity, but the path towards a clinically meaningful therapeutic is uncertain. Lp(a) is largely genetically determined, often elevated from early life and not meaningfully lowered by lifestyle modification or statin therapy, making it a distinct source of lifelong residual atherothrombotic risk. At the commonly used threshold of >50 mg/dL, elevated Lp(a) is estimated to affect approximately 1.4 billion people, or around one in five individuals globally.²⁵ As shown in Figure 8, four of the five selected programmes have reached Phase III development and collectively span three modalities: an antisense oligonucleotide, siRNA therapeutics and an oral small molecule. Across separate studies, pelacarsen, muvalaplin, zerlasiran, lepodisiran and olpasiran have reported reductions in circulating Lp(a) of approximately 80% to 97%. These results should not be interpreted as a head-to-head comparison, because trial populations, dosing regimens, follow-up periods and reporting methods differ. Despite these cross-trial differences, the magnitude of the reductions demonstrates that substantial pharmacological lowering of Lp(a) is achievable through several therapeutic approaches.

Figure 8: Clinical landscape of Lp(a) lowering drugs



*Primary endpoint not met; detailed results pending
**Phase III trial start delayed

Abbreviations: ASO – antisense oligonucleotides; siRNA – small interfering ribonucleic acids; MACE — major adverse cardiovascular event
Source: Company press releases; IQVIA Thought Leadership

The key question is no longer whether Lp(a) can be lowered, but whether lowering it reduces major adverse cardiovascular events. In September 2026, Novartis reported that pelacarsen lowered Lp(a) in the Phase III Lp(a)HORIZON trial, but the study did not meet its primary four-component cardiovascular endpoint.¹⁰ Detailed results were not yet available at the time of writing, limiting our ability to draw strong conclusions. Even so, the primary-endpoint miss represents a major setback for the field and raises the bar for the entire class. The other ongoing CV outcome trials OCEAN(a)-Outcomes, OCEAN(a)-PreEvent, ACCLAIM-Lp(a) and MOVE-Lp(a) will test whether cardiovascular benefit can be demonstrated with other agents or in different populations.

If these trials demonstrate cardiovascular benefit, population-level impact will still depend on effective testing and care pathways. Lp(a) testing is not routine, creating a substantial patient-identification challenge for future therapies. Recommendations to measure Lp(a) at least once in adulthood are now reflected in major European and US guidance, yet awareness is limited, and many healthcare systems

lack clear pathways for interpreting elevated results and translating them into clinical action.^{26,27} Successful implementation will require Lp(a) testing to be integrated into routine cardiovascular risk assessment, supported by clear treatment thresholds and coordinated pathways across primary and specialty care.

Commercially, Lp(a) remains a potential opportunity, but the case for broad category creation has been materially weakened. The pelacarsen primary endpoint miss creates meaningful read-through risk for the wider class and raises the evidence bar for the other outcomes programmes. High prevalence and the absence of approved targeted therapies support long-term potential, but any viable market now depends on independent outcomes validation and may be narrower, slower to emerge and concentrated in clearly defined high-risk populations. Differences in modality, potency, patient population and endpoint design leave room for success, but provide differentiation rather than insulation from HORIZON. Clinical validation alone, however, would not determine the size of the commercial opportunity. Treatment eligibility

and uptake will be shaped by approved indications, demonstrated effect size, absolute cardiovascular risk reduction, testing penetration, guideline placement, route and frequency of administration, price, reimbursement and evidence of cost-effectiveness. New Lp(a) therapies will also enter a treatment landscape shaped by statins and other low-cost lipid-lowering therapies with decades of outcomes and real-world evidence, setting a high bar for widespread uptake. Health systems and payers will require not only proof of cardiovascular benefit on top of standard of care, but also evidence that testing programmes, risk-stratification approaches and treatment pathways deliver value at a population level.

Lp(a) remains an important cardiovascular risk marker, but the therapeutic case for lowering it is still unproven. Any future therapy will need to show meaningful cardiovascular benefit in a clearly defined patient population, not simply a large reduction in Lp(a). Success will also depend on finding eligible patients, securing reimbursement and building care pathways. For now, the broad category creation is possible, but far from certain.

II. Hypertension

INNOVATION LANDSCAPE

High blood pressure affects 1.4 billion people globally and is the number one risk factor for all-cause mortality, for example leading to ischaemic heart disease, heart failure, stroke, chronic kidney disease or dementia. In 2023, 11 million deaths were attributed to hypertension, or 16% of all deaths worldwide.^{28,29}

The current hypertension pipeline, excluding pulmonary hypertension, comprises 116 clinical-stage assets, including 44 in phase 1, 25 in phase 2, 34 in phase 3 and 13 at pre-registration. Combination therapies account for 20% of the hypertension pipeline, with many of those exploring new fixed-dose combinations (FDCs) of multiple, often off-patent actives.

These innovation efforts explore a range of mechanisms of action and modalities to target both well-established and emerging pathways associated with hypertension.

The Renin–Angiotensin–Aldosterone System (RAAS), as the primary regulator of blood volume, electrolyte homeostasis and systemic vascular resistance, has been the principal target of existing, foundational anti-hypertensive drugs, including beta blockers, renin inhibitors, angiotensin converting enzyme (ACE) inhibitors, and angiotensin II type receptor blockers (ARBs).



Novel therapeutic approaches seek to improve on legacy, RAAS-mediating drugs through greater precision, selectivity and extended durability to address unmet needs, e.g., uncontrolled, resistant hypertension or primary aldosteronism.

- By directly targeting CYP11B2, the enzyme responsible for aldosterone synthesis, highly selective **aldosterone synthase inhibitors** (ASI), such as baxdrostat, lorundrostat, dexfadrostat phosphate, hold great promise for treating uncontrolled or resistant hypertension, and primary aldosteronism. For example, AstraZeneca's baxdrostat, recently approved by the FDA as Baxfendy, reduced systolic blood pressure (SBP) at week 12 by 9.8 mmHg (placebo-adjusted) in the BaxHTN phase 3 trial, while demonstrating the ability to control ambulatory SBP over a 24-hour period in patients with treatment-resistant hypertension in the phase 3 Bax24 study.^{30,31,32}
- **Non-steroidal mineralocorticoid receptor antagonists** (nrMRA) seek improved selectivity and safety over older steroidal MRAs such as spironolactone. Non-steroidal MRA esaxerenone is approved for hypertension treatment in Japan and has demonstrated potent and sustained antihypertensive effects in different patient populations, including those with moderate renal impairment, type 2 diabetes with albuminuria and severe hypertension.³³ Bayer's nrMRA finerenone, approved as Kerendia for CKD and heart failure, offers modest SBP reduction but significant broader cardiorenal protection, in particular for patients with diabetes and chronic kidney disease.
- **Hepatic angiotensinogen (AGT) inhibition** represents an upstream intervention in RAAS to block the downstream signalling cascades triggered by angiotensin type 1 (AT1) and type 2 (AT2) receptors. Subcutaneous, **small interfering RNA** (siRNA) zilebesiran (Roche/Alnylam), with 6-monthly dosing, achieved durable suppression of serum AGT

and reduced 24-hour ambulatory SBP by 15 mmHg vs. placebo after 3 months in the KARDIA-1 phase 2 trial. The anti-hypertensive effect was sustained over 6 months following a single injection. Zilebesiran has progressed to phase 3, with the ZENITH global cardiovascular outcomes trial (CVOT) enrolling 11,000 patients with uncontrolled hypertension.³⁴

An alternative approach utilising antisense oligonucleotides (ASOs) targets mRNA to inhibit the translation of AGT protein. In the KARDINAL phase 2 trial, ASO therapeutic tonlamarsen (Ionis/Kardigan) demonstrated a statistically significant reduction in plasma AGT levels and a clinically meaningful reduction in in-office SBP from baseline to week 20.³⁵ A phase 2b trial investigating tonlamarsen in patients with acute severe hypertension (ASH) is expected to start later in 2026.³³

Looking beyond RAAS, endothelin-1 is a potent vasoconstrictor that acts on two receptors, type A (ETA) and type B (ETB), and plays a key role in the pathogenesis of hypertension, thus making it another promising therapeutic target. Idorsia's **dual ETA/ETB receptor antagonist** apocritentan is approved for the treatment of resistant hypertension. In the phase 3 PRECISION trial, a 25mg dose reduced office SBP by 15.2 mm Hg in resistant hypertension, which was sustained through 40 weeks.³⁶

Atrial natriuretic peptide is involved in the long-term regulation of sodium and water balance, blood volume and arterial pressure.³⁷ However, short half-life has limited therapeutic applications to date. Instead, augmentation of the natriuretic peptide system by inhibiting neprilysin, a key enzyme for degradation, has proven effective in lowering blood pressure. For example, Entresto, a fixed dose combination of neprilysin inhibitor sacubitril and ARB valsartan, demonstrated a significant antihypertensive effect over ARB olmesartan, including a superior, sustained blood-pressure-lowering effect over 24 hours. Entresto is approved for the treatment of hypertension in China, Japan and South Korea.^{38,39}

Novel therapeutic approaches seek to improve on legacy, RAAS-mediating drugs through greater precision, selectivity and extended durability to address unmet needs

Other exploratory MoAs in preclinical or early-stage development include aminopeptidase A inhibitors, AT2 receptor agonists, ACE2 activators, angiotensin-(1-7) analogues and nicotinamide adenine dinucleotide (NAD+) supplementation.³¹ The role of inflammation, immunity and oxidative stress in the initiation and evolution of hypertension is increasingly being recognised, which opens the door for potential novel therapeutic strategies.⁴⁰

Beyond the development of de novo pharmacotherapies, some companies look to fixed-dose combinations (FDC) of multiple, established antihypertensive agents to reduce the pill burden on patients with the aim to improve adherence. For example, Servier is developing triple- and quadruple-combinations in a single pill, including a beta blocker, ACE inhibitor, calcium channel blocker with or without a diuretic.⁴¹

CONTROLLING HYPERTENSION: BEYOND PHARMACOTHERAPEUTIC INNOVATION

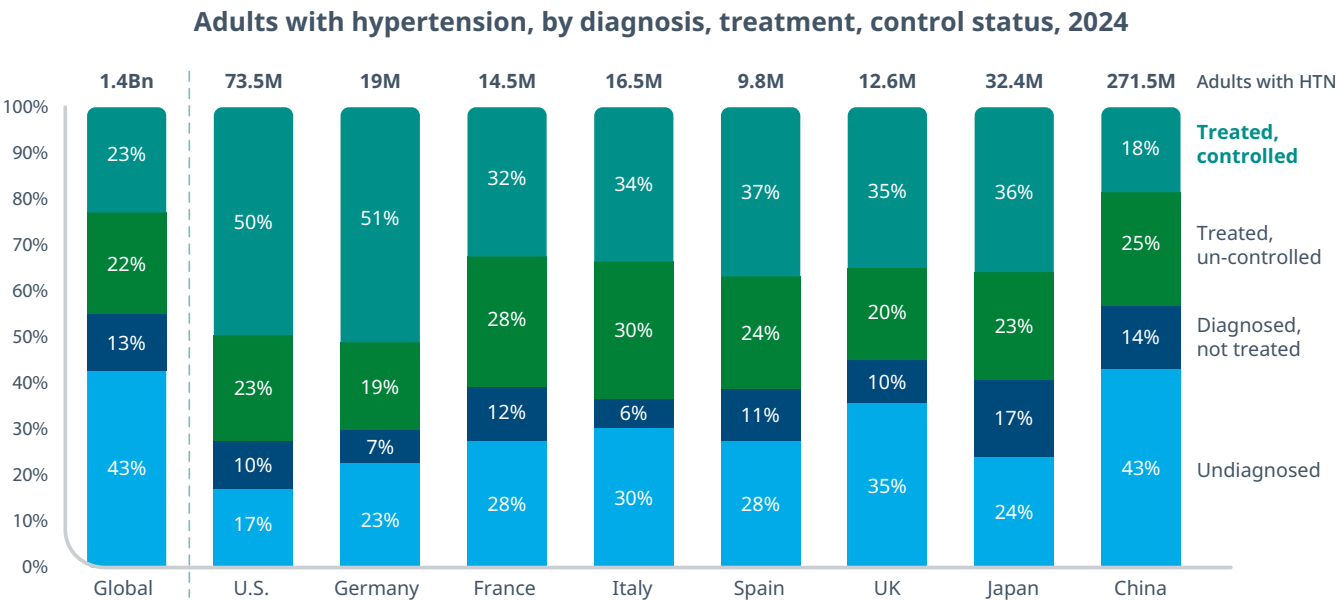
Hypertension is the leading global cause of premature death. Crucially, it is also a preventable risk that makes achieving sustained blood pressure control, at population level, a public health concern.

Despite the availability of long-established, now off-patent antihypertensive therapies, elevated blood pressure remains a major health burden in both developed and developing countries.

Global blood pressure control rates are still disconcertingly low, at ~23% of adults affected by hypertension, and ~50% for those being treated. Even among high-income countries, very few achieve control rates of 50% for their respective hypertensive adult populations, while many find themselves in the 35-45% range (see Figure 9).²⁶

Despite the availability of long-established, now off-patent antihypertensive therapies, elevated blood pressure remains a major health burden in both developed and developing countries

Figure 9: Hypertension remains poorly controlled, even in treated patients



Source: WHO, Global report on hypertension, 2025

Pharmacotherapeutic innovation alone is not enough to close the hypertension control gap, and it can only be a part of a wider solution.

Achieving population level control of hypertension requires addressing systemic barriers, for example, significant underdiagnosis of an asymptomatic condition; crude diagnostic approaches that do not reflect the heterogeneity of hypertension, e.g., multiple comorbidities or different endotypes; therapeutic inertia including inadequate titration and delayed intensification; and health inequities, with hypertension disproportionately affecting disadvantaged populations. Furthermore, among treated patients, non-adherence is one of the major drivers of poor blood pressure control.

Achieving population level control of hypertension requires addressing systemic barriers

Policymakers must therefore elevate hypertension control and prevention as a health priority, strengthen primary care delivery and equip health systems to treat hypertension as part of the CVRM disease continuum, including population screening with CVRM risk stratification, matching therapies to risk profiles and patient endotypes, ensuring equitable access to care, and utilising less burdensome, patient-friendly regimens combined with digital health tools to dramatically boost adherence.

For example, wearables have the potential to transform hypertension detection and management via continuous risk monitoring while facilitating a shift to community-based, preventive, and digitally enabled care. Once such digital tools have been clinically validated, with proven real-world reliability, embracing digital blood pressure monitoring at scale – alongside strategies addressing other modifiable causes – holds significant promise for transforming prevention of cardiovascular disease, much as cancer screening revolutionised the prospects for patients in oncology.⁴²

Outlook for the CVRM market

Cardiovascular-renal-metabolic diseases collectively represent a sizeable, global market worth \$384 billion in 2025, at ex-manufacturer prices, including obesity which accounted for \$66 billion.

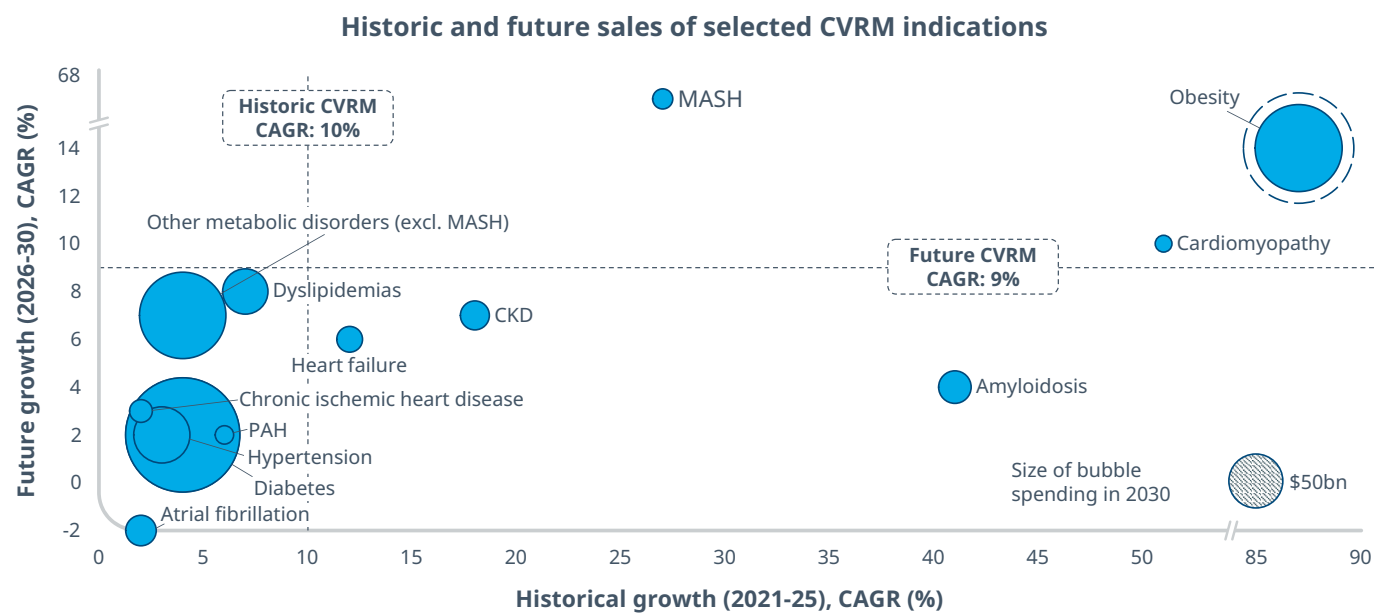
Excluding obesity, we forecast compound annual growth at 9% for 2026-2030, a slight decline from the historical CAGR (2021-2025) of 10%, with the collective, ex-obesity CVRM market set to reach \$418 billion globally by 2030.

If we include obesity, the total CVRM market is forecast to reach \$543 billion by 2030, equating to compound annual growth of 9% for 2026-2030 vs. a historical CAGR (2021-2025) of 15% for this CVRM market definition. This slowdown reflects an evolving obesity market that has become more established and moved beyond its initial hyper-growth phase, historically delivering >85% CAGR (2021-2025), with future obesity growth now forecast at 14% CAGR (2026-2030).



Since CVRM is a broad umbrella that comprises a diverse set of diseases with different underlying epidemiological dynamics and great variation in unmet needs and maturity of the respective therapeutic landscapes, it is not surprising that we find a wide range of disease-specific growth trajectories (see Figure 10).

Figure 10: CVRM market dynamics



Note: Historic and future CAGRs were calculated based on the CVRM market excluding obesity
Source: IQVIA Institute Report 'Global Use of Medicines Outlook to 2030'; IQVIA Forecast Link, accessed August 2026

For example, MASH is being transformed by disease-modifying treatments. Following the FDA approval in March 2024 of Rezdiffra as the first MASH-specific therapy, high pent-up demand has translated into rapid product uptake in the US, and in turn accelerated growth of the MASH market. Semaglutide has since become the second MASH-specific therapy to enter this market, while a rich pipeline comprising multiple late-stage assets will fuel future growth as unmet need remains high.

Similarly, as we elaborated earlier in one of the deep dive sections, dyslipidaemia is also benefiting from therapeutic innovation that will sustain its growth trajectory despite the drag of high utilisation of low-cost generics, e.g., statins, in this market.

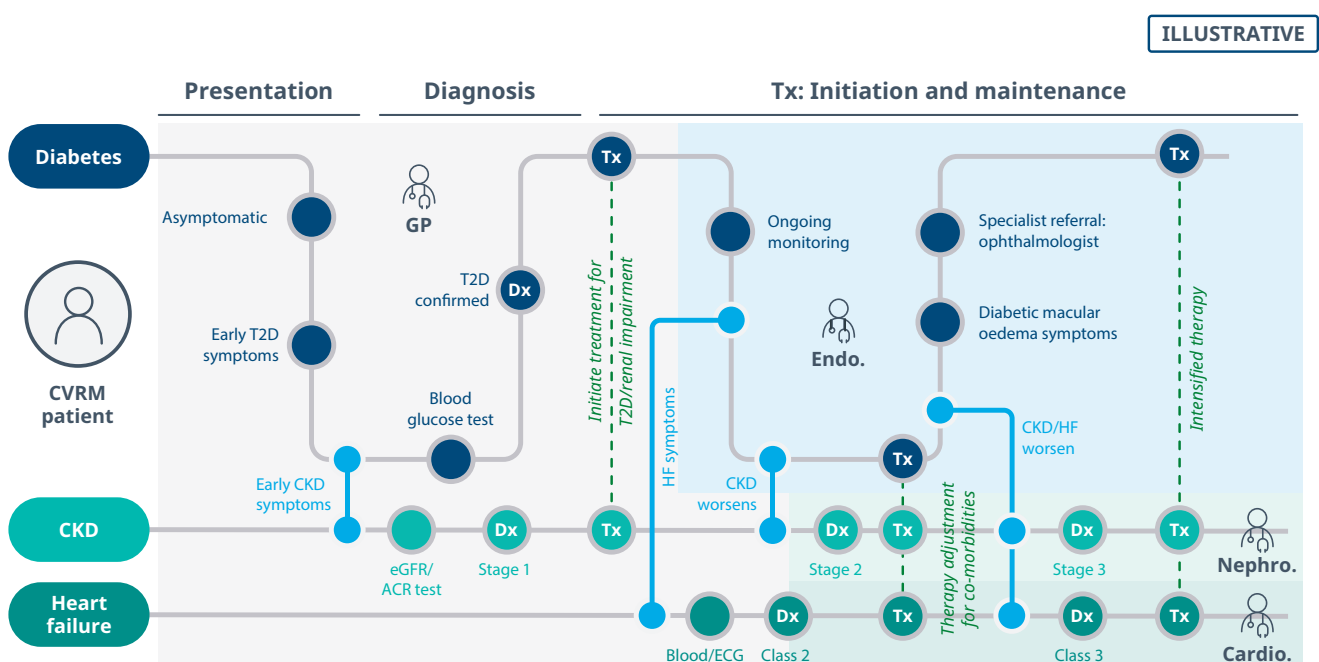
Innovators therefore must look beyond headline growth figures, even within an indication, because pockets of high growth potential co-exist with less dynamic, stagnant or even declining market segments that otherwise might mask CVRM opportunities.

How to succeed as CVRM innovator

Innovators face a range of specific challenges to the adoption and successful commercialisation of novel CVRM therapies:

- Utilisation of generics, including those of former blockbuster brands, is high across many cardiovascular-renal-metabolic conditions, e.g., reaching 80% volume share in dyslipidaemia or hypertension. These agents are not only inexpensive but also backed by decades of real-world data around their health benefits. This sets a dual barrier for innovators: it anchors price points on low comparators and raises the evidence bar, since a new class arrives with wider confidence intervals, higher prices and no comparable real-world track record.
- Faced with innovation aimed at high prevalence conditions, such as obesity, cardiovascular disease, hypertension, dyslipidaemia or CKD, payers are concerned about the budget impact of novel therapies. In response, payers typically seek to tightly restrict access while adopting a ‘good enough’ mindset that doesn’t recognise true unmet need.
- To support a new CVRM therapy’s adoption, key stakeholders expect to see cardiovascular outcomes data, e.g., reduction in MACE-3 risk, as the ultimate measure of clinical benefit. Outcomes trials to generate such data are risky, typically require large sample sizes to be adequately powered while running for extended periods of time.
- CVRM innovation may not fit with established clinical practice or care pathways, e.g., introducing a parenterally administered biologic therapy into an indication with an oral standard of care; crossing different settings of care involving referrals from GPs to specialists; or requiring novel diagnostics that are not embedded in routine practice, e.g., testing for biomarkers such as hsCRP, Lp(a) or imaging techniques to diagnose MASH.
- CVRM patient journeys are uniquely complex due to interdependencies between different co-morbidities, which manifest themselves at different time points in the natural history of disease, and inevitably lead to an expansion of HCP specialties involved at different stages in a patient’s care (see Figure 11).

Figure 11: Interconnected CVRM patient journey



Source: IQVIA Thought Leadership

Therefore, CVRM innovators must address five strategic priorities to achieve commercial success:

- 1. Extensive, early market shaping:** Early engagement of a broad range of stakeholders, including payers, external experts, patients, patient advocacy groups and policy makers is essential to build advocacy. Policy makers are particularly important stakeholders for recognising and elevating CVRM diseases as a public health priority for managing population health to secure adequate and sustainable funding for the adoption of innovation.
- 2. Evidence leadership:** Demonstrating patient- and health-system-relevant value relative to an entrenched, low-cost standard of care is critical for CVRM innovation. This will require proactively planning for long-term outcomes data, e.g., via CVOTs, and/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).
- 3. Reassured payers:** Innovators will need to provide strong evidence to prove value to payers and to address budget impact concerns, by clearly defining discrete target populations linked to superior outcomes which are identifiable in routine clinical practice. Furthermore, innovators must ensure transparency of responsible pricing which reflects both differential value and patient volume.

Learning from the rapid emergence of the sizeable, self-pay market in obesity, CVRM innovators should also consider novel approaches for suitable indications, e.g., initially launching in the private/self-pay market before transitioning to reimbursement, or exploring subscription models.
- 4. Health system readiness:** 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 ensure treatment-eligible patients are identified as a key prerequisite to therapy adoption.
- 5. Patient engagement:** Achieving optimal patient outcomes in chronic CVRM conditions requires ongoing engagement alongside pharmacotherapy, e.g., via telehealth or digital health solutions, to support patients in dealing with the practicalities of day-to-day living with the condition, restore agency and to facilitate behavioural change, including diet, lifestyle and improved adherence and persistence with prescribed treatment. Digital health tools in particular could offer unique engagement opportunities at scale, e.g., expanding wellness devices beyond sleep scores or glucose measurement to monitor CV markers in a mass-market segment of motivated, affluent patients and consumers.

As the leading causes of mortality and morbidity globally, CVRM diseases are an indisputable public health priority and thus a worthwhile focus for biopharma innovators. Propelled by recent commercial successes and sustained innovation momentum, the remarkable cardiometabolic renaissance will not lose steam any time soon.

About the authors



MARKUS GORES

Vice President, Thought Leadership, IQVIA

Markus has over 20 years of experience in life sciences, advising clients in all major geographies on a broad range of topics, including real world evidence strategy, launch readiness, go-to-market models, brand and commercial strategies, and building enabling organisational capabilities. Markus is a frequent speaker on the latest industry trends and regularly engages with senior leadership teams of pharmaceutical companies.

Prior to his current role in Thought Leadership, he has held leadership positions within IQVIA Real World Solutions and QuintilesIMS Consulting Services (formerly the IMS Consulting Group). Markus holds a PhD in Pharmaceutical Chemistry from the University of Hanover and has completed post-doctoral research at the University of California.



STEFAN LUTZMAYER

Senior Consultant, Thought Leadership, IQVIA

Stefan has over 9 years of experience working in academia and life sciences. He joined the Thought Leadership team in 2021 where he creates novel materials on emerging next-generation biotherapeutic platforms like the microbiome or gene-editing, new developments across therapeutic areas, including central nervous system or cardiometabolic diseases as well as vaccines and cold chain pharmaceuticals. Stefan is considered a subject matter expert in these areas. He frequently engages with senior client stakeholders, speaks at conferences, and supports consulting projects.

Stefan has prior experience working as an IT consultant advising healthcare and life sciences clients. He holds a PhD degree from the University of Vienna, is trained in molecular biology and data analysis and has published multiple peer-reviewed articles in internationally-renowned journals.



SOPHIE MARLOW

Intern, Thought Leadership, IQVIA

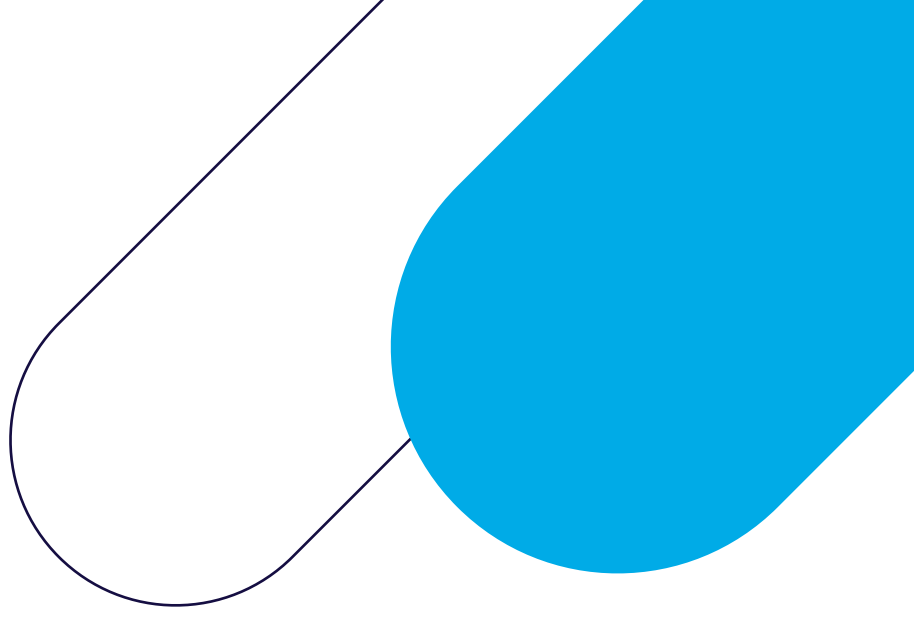
Sophie is a PhD candidate in Cardiovascular Science at the University of Oxford, funded by the British Heart Foundation. Her research applies molecular biology and emerging sequencing technologies to identify and characterise gene regulatory mechanisms underlying cardiac development. During her PhD, Sophie is undertaking an internship with the Thought Leadership team, bringing her scientific expertise and research experience to emerging topics across the life sciences. Prior to her PhD, Sophie completed an MBiochem in Molecular and Cellular Biochemistry, also at the University of Oxford.

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