

Weighing the Evidence

Quantifying the mortality and morbidity impacts of GLP-1 and other incretin-based drugs in the US, UK, Canada, and Hong Kong populations

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Executive summary

RGA has quantified the expected mortality and morbidity impacts of incretin-based drugs, including GLP-1s, approved as anti-obesity medications (AOMs) and diabetes treatments in the US, UK, Canada, and Hong Kong.

In this report, we share:

- Expected population-level mortality and morbidity impacts for these four markets under central, optimistic, and pessimistic scenarios.
- Expected population level mortality impacts by age under the central scenario.
- Views on how the impacts of these treatments for obesity and diabetes could exceed those projected in the central scenario and the potential for further reductions in mortality and morbidity as the therapeutic landscape for incretin-based drugs expands beyond obesity and diabetes.
- Considerations for how to incorporate these insights into future improvement bases
- Underwriting and claims considerations

Key findings

1. At the general population level, AOMs will have a meaningful impact on mortality. This will differ by geography, largely reflecting the obesity profiles of different markets, and by age, sex, and access to the drugs.

We model the impact of AOMs over the next 20 years to 2045 with reference to three key groups of assumptions: effectiveness, uptake, and relative risk of mortality and morbidity. We calculate optimistic and pessimistic scenarios by flexing these key assumptions to plausible higher and lower values. The table below shows the expected mortality impact of these scenarios at the population level.

Table 1: Cumulative population mortality improvements over 20 years to 2045 due to AOMs under three scenarios compared to our baseline scenario

Market	Pessimistic	Central	Optimistic
US	1.0%	3.5%	8.8%
UK	0.5%	2.0%	5.3%
Canada	0.7%	2.6%	6.4%
Hong Kong	0.4%	1.4%	3.9%

Average across males and females ages 20-90.

It is important to recognize that the impact of AOMs will vary by age, reflecting differences in obesity levels, the mortality risk associated with obesity, and differences in uptake. The table below shows the expected mortality impact in our central scenario by market and by age.

Table 2: Cumulative population mortality improvement impacts over 20 years to 2045 due to AOMs by market and age

Age band	Central scenario			
	US	UK	Canada	Hong Kong
20-44	3.5%	3.1%	3.0%	2.1%
45-59	5.1%	4.2%	4.0%	2.1%
60-74	4.6%	3.1%	3.8%	1.6%
75-84	2.6%	1.2%	2.0%	1.2%
85-100	1.8%	0.9%	1.2%	0.8%
20-90	3.5%	2.0%	2.6%	1.4%

Average across males and females.

2. AOMs will likely have a smaller impact on general population morbidity.

We define morbidity as the incidence of claims under a typical critical illness product. Cancer is the largest single cause of morbidity incidence in critical illness products. While reducing body mass index (BMI) does reduce the risk of cancer incidence, it is not to the extent that lowering BMI reduces mortality risk. Therefore, we expect morbidity impacts to be generally smaller than the corresponding mortality impacts.

Table 3: Cumulative population morbidity improvements over 20 years to 2045 due to AOMs under three scenarios

Market	Pessimistic	Central	Optimistic
US	0.6%	1.8%	5.0%
UK	0.3%	1.0%	2.9%
Canada	0.4%	1.5%	4.2%
Hong Kong	0.1%	0.4%	1.2%

Average across males and females, ages 20-90.

3. Insured groups are likely to see somewhat lower mortality and morbidity impacts than the general population. Lower average BMI means less scope for improvements, even though insureds have greater access to the drugs.

Insured lives and annuitants typically come from a higher average socioeconomic group than the general population and generally are expected to have a lower average BMI. Insured lives are also typically underwritten and have a different mix of causes of mortality and morbidity than the general population. Our model projects that the lower average BMI for insured groups has more impact than the increased ability to access the drugs, and so the overall mortality and morbidity impact is typically lower than for the general population. The actual impact AOMs will have will reflect the characteristics of a life and health insurer's insured portfolio.

4. An insurer's current mortality trend assumptions likely include anticipated improvements from drivers such as medical advances. It may be too early to make material adjustments to those assumptions for AOMs, but they increase confidence in future mortality and morbidity improvements.

RGA's study results described so far reflect changes to current mortality and morbidity rates. When translating to impacts on assumptions, it is important to consider that (re)insurers already assume positive improvements in the future. Anti-obesity medications are a tangible advance contributing to these future improvements.

5. This is a fast-moving space with significant uncertainty. Model assumptions will need refining as new evidence emerges and as new indications for the drugs are approved.

The upside potential of these drugs is exciting, but challenges linked to safety, side effects, access, and adherence need to be overcome to achieve the full impacts we anticipate.

While cost is currently a barrier to uptake, growing competition and the arrival of generic and oral formulations are expected to lower costs significantly. The next wave of incretin-based therapies is poised to offer significant advantages over the current generation for treating diabetics and for weight loss in those living with obesity. We have already anticipated some of these developments, but this is a fast-moving space, and we will continue to review model assumptions accordingly.

Incretin-based drugs are now being investigated – and in some cases approved – for a wide range of conditions, including cardiovascular disease, neurodegenerative disorders, and even substance use disorder. As approved indications continue to broaden, and adoption scales in those with established disease, the cumulative impact on public health could be profound.

There is also growing interest in the potential role of incretin-based drugs as preventive medicines. Their systemic anti-inflammatory effects, metabolic regulation, and influence on satiety and insulin sensitivity suggest they could help prevent the onset of multiple chronic conditions. If these benefits extend to individuals without established disease, we could see a significant reduction in morbidity and mortality across the general population.

6. Insurers should consider the impact on business, including pricing and reserving assumptions, new policyholder behaviors, underwriting, and claims.

Our companion paper, [“Evaluating Biometric Trend Drivers: How to reflect medical breakthroughs and other drivers in forward-looking assumptions,”](#) explores the practicalities for insurers in maintaining an up-to-date view on emerging biometric trend drivers such as AOMs and provides a framework for incorporating the insured mortality impacts into their insured improvement bases.

The use of AOMs introduces the risk of anti-selective policyholder behavior, as individuals who have lost considerable weight may lapse their rated policies and re-enter with better terms. As such, insurers may not capture the full economic benefit of improved mortality and morbidity.

The increasing use of AOMs will significantly influence underwriting risk assessment. As evidence accumulates, underwriting approaches must evolve to recognize improvements while maintaining vigilance to validate these therapies’ potential.

Accurate disclosures at the underwriting stage may need to be validated at the claims stage, and claims assessors will require a deep understanding of the use of AOMs to ensure accurate interpretation of disclosures made as part of the insurance application.

The impact on insureds reflects the characteristics of the insured book. To explore insured impacts further, and how they may translate to your policyholders, reach out to your local RGA representative.

Part 1. The obesity epidemic and the arrival of next-generation anti-obesity medications (incretin-based therapies)

The obesity epidemic: A global health issue

Obesity¹ is a multifactorial, chronic disease with significant consequences for physical and psychological wellbeing. The obesity epidemic is a major public health issue that has escalated over many decades. According to the Global Burden of Disease study, in the US, between 1990 and 2021, obesity prevalence more than doubled in adults and almost tripled in adolescents. We estimate 43% of the non-diabetic adult US population in 2025 is obese. In a scenario without AOMs, we estimate this could rise to 49% by 2045.

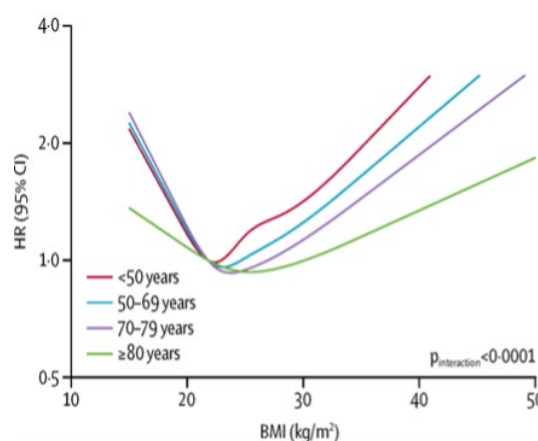
The obesity epidemic is not limited to the US. It is a global concern, with more than a billion people living with obesity around the world, according to estimates published in *The Lancet* in 2024. From 1990 to 2022, the worldwide rate of obesity more than doubled in women, nearly tripled in men, and quadrupled among children and adolescents.

Understanding the mortality burden of the obesity epidemic

Obesity is associated with numerous health complications, including type 2 diabetes, cardiovascular disease, metabolic dysfunction-associated steatotic liver disease (MASLD), and certain cancers. Furthermore, obesity is strongly associated with higher mortality risks for various causes. Many studies have shown a U- or J-shaped relationship between BMI and mortality, where lower and higher BMI are associated with increased mortality risk compared to “normal weight” BMI levels (defined as a BMI between 18.5 to 25 kg/m²); see Figure 1 taken from a [population-based cohort study of 3.6 million adults in the UK](#).

In a [2022 study](#), researchers suggested elevated body weight was responsible for almost 500,000 excess deaths in the US in 2016 alone (a loss in life expectancy of nearly 2.4 years). Furthermore, a [2018 study](#) using NHANES data modeled the impact of obesity on mortality improvement between 1988 and 2011 and found that rising BMI levels reduced mortality improvement in the US by more than 0.5% per annum. The economic burden of obesity is also substantial, with increased healthcare costs and lost productivity.

Figure 1: Association between BMI and all-cause mortality among never-smokers by age



This age-stratified analysis suggests that the relationship between higher BMI and all-cause mortality is attenuated by age. It is also evident that the nadir for all-cause mortality risk shifts higher for older ages. Creative Commons CC-BY license.

¹ Defined as a BMI of 30 or higher in the US, Canada, and UK, or 25 or higher in Hong Kong.

Incretin-based anti-obesity medications

The development of next-generation AOMs, such as incretin-based GLP-1 receptor agonists, offers promising potential for reducing the health impacts of obesity and improving overall public health outcomes.

Incretin-based drugs are medications that mimic or enhance the action of incretin hormones, which are naturally released by the gut after eating to help regulate blood sugar and appetite. The two most significant incretin hormones are GLP-1 (glucagon-like peptide-1) and GIP (glucose-dependent insulinotropic polypeptide). These hormones stimulate insulin release in response to food, suppress glucagon (which raises blood sugar), and slow gastric emptying to promote satiety (feeling full).

GLP-1 receptor agonists (RAs) were originally developed to treat type 2 diabetes mellitus (T2DM) and have been FDA-approved for this indication since 2005. Incretin-based therapies, including GLP-1 RAs, have since expanded their therapeutic indications beyond diabetes care to weight management.

The first incretin-based drug approved specifically for weight loss was liraglutide (Saxenda), developed by Novo Nordisk. It received US Food and Drug Administration (FDA) approval in 2014 for chronic weight management in adults with obesity or overweight and with at least one weight-related condition.

Since then, more potent GLP-1 and dual agonists (targeting both GLP-1 and GIP) have been approved, including for weight loss in those living with obesity. Semaglutide (Wegovy) was approved in 2021 and tirzepatide (Zepbound) in 2023.

Impressive weight-loss results in clinical trials

In 2015, the [SCALE trial](#) results demonstrated the effectiveness of once-daily injections of liraglutide (Saxenda). The 56-week trial involved patients without type 2 diabetes and a BMI of at least 30 (or a BMI of at least 27 if they had treated or untreated dyslipidemia or hypertension); patients also received counseling on

lifestyle modification. The trial showed that liraglutide, as an adjunct to diet and exercise, was associated with reduced body weight (mean weight loss was 8%) and improved metabolic control.

In 2021, results from the [STEP-1 trial](#) were published. This landmark study evaluated the efficacy of semaglutide (Wegovy) and found it delivered significantly greater weight reduction than liraglutide (Saxenda) – 15% mean weight loss over 68 weeks.

Tirzepatide (Zepbound), a dual GLP-1/GIP agonist, further raised the bar, with mean weight loss exceeding 20% in the [SURMOUNT-1 trial](#).

Impressive trial results... complex realities

Despite the promise of incretin-based therapies, achieving similar outcomes outside of clinical trials has been challenging. Cost remains a major barrier in many markets, with monthly prices in the US ranging from \$500 to over \$1,000, and insurance coverage often limited to patients with diabetes. Adherence is another major issue – [one study](#) suggested that roughly two-thirds of patients discontinue GLP-1 therapy within the first year, often due to high costs, gastrointestinal side effects, lack of perceived benefit, or difficulty maintaining lifestyle changes. Moreover, the supportive infrastructure seen in trials – such as regular coaching, nutrition guidance, and follow-up – is often missing in routine care.

The [STEP 1 extension trial](#) highlights the importance of treatment adherence. The trial investigated the effects of stopping semaglutide treatment in people with obesity. Following 68 weeks of once-weekly semaglutide (2.4 mg), participants had achieved an average 17.3% reduction in body weight. However, after discontinuing both the drug and lifestyle support, participants regained approximately two-thirds of their lost weight over the next year – leaving a net weight loss of just 5.6% from baseline. Importantly, the cardiometabolic improvements seen during treatment – such as healthier blood pressure, cholesterol, and glucose levels – also reverted toward baseline after withdrawal. The SURMOUNT-4 trial revealed a similar phenomenon for Tirzepatide.

These findings reinforce the view that obesity is a chronic, relapsing condition, and that ongoing treatment may be necessary to sustain the health benefits achieved with incretin-based therapies.

Loss of lean muscle mass during rapid weight loss is a growing concern. Studies suggest that 25-40% of weight lost on GLP-1 therapies may come from lean tissue, including skeletal muscle and bone. This is particularly problematic for older adults, as it can lead to sarcopenia, reduced strength, impaired mobility, and increased risk of falls and fractures. Without structured resistance training, increased protein intake, and body composition monitoring, patients may lose not just fat but vital skeletal muscle and bone – undermining long-term health outcomes.

As these therapies move into broader use, addressing these real-world complexities will be essential to realizing their full potential. A multimodal approach is likely needed – one that combines medication with nutrition support, physical activity, and ongoing clinical oversight.

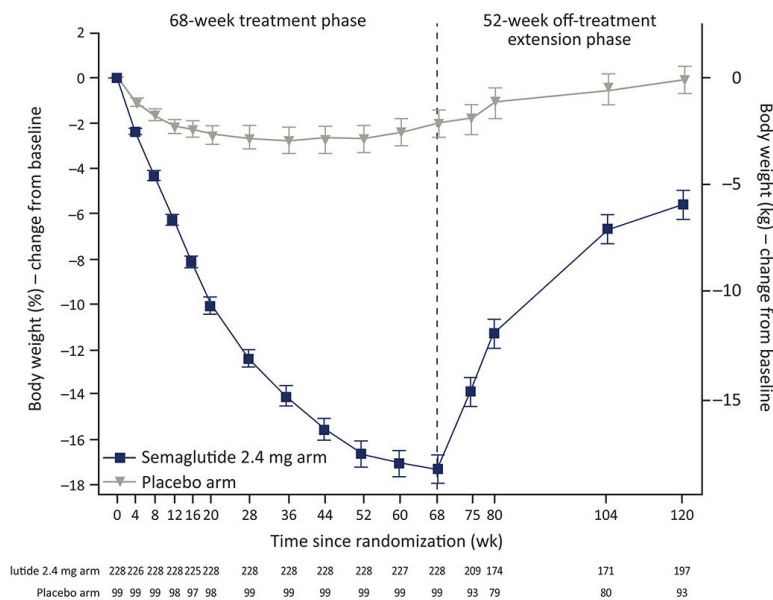
Furthermore, these drugs are not a panacea for the obesity epidemic, as comprehensive solutions must also address underlying behavioral, social, and environmental factors. Fully addressing the obesity epidemic requires a multifaceted approach, including public health initiatives, policy changes, and individual lifestyle modifications.

More exciting health benefits and indication approvals to come?

Incretin-based therapies are increasingly recognized not only for their weight-loss effects but also for their broader health benefits. Clinical trials and meta-analyses have shown that these drugs significantly improve glycemic control, reduce blood pressure, and positively impact lipid profiles, even in patients without diabetes.

Indications for incretin-based therapies are expanding beyond diabetes and weight management. There is a growing pipeline of approvals – including for cardiovascular disease – and emerging promise in other areas, such as Alzheimer’s disease, cancer, and addiction. These drugs are increasingly recognized not only for their therapeutic benefits but also for their potential to prevent serious chronic conditions. See Part 3 for an exploration of the many exciting possibilities that incretin-based therapies may yet unlock.

Figure 2: Change from baseline in body weight by week for all participants in the STEP-1 trial



Weight regain and cardiometabolic effects after withdrawal of semaglutide. Creative Commons CC-BY license.

Part 2. Modeling the potential impact of incretin-based therapies as weight-loss and diabetes treatments on population morbidity and mortality trends

The RGA model

Quantifying potential impacts of incretin-based therapies on mortality and morbidity outcomes is difficult, given the many uncertainties at play; however, the long-term nature of many insurance and annuities contracts makes it imperative to estimate the effects of this emerging medical breakthrough on future mortality and morbidity assumptions.

To this end, RGA developed a model to assess the potential impact of these drugs – as treatments for weight loss in obese population, and for diabetes – on population mortality and morbidity,² revealing significant potential reductions in cardiovascular incidence and mortality rates.

Important assumptions to consider when quantifying the impacts of these therapies as a weight-loss treatment in obese populations include:

- **Effectiveness** – The amount of weight an individual taking the drug is expected to lose, and the timeframe over which they are expected to lose it. It also covers the extent of weight expected to be regained on cessation of treatment.
- **Uptake** – The use of these medications in different age groups and in different weight classes. We allow for anticipated increases in uptake as new medications are approved, costs are reduced, and better side-effect profiles are realized.
- **Persistency** – The length of time we expect patients to remain on the medication.
- **Relative risk of mortality and morbidity** – The level of mortality and morbidity reduction we expect for

those taking AOMs. Most of this can be explained by the link between weight and risk described in Part 1, but we also allow for mortality improvements observed in clinical trials that cannot be predicted from weight-loss alone. For example, the SELECT trial showed a 20% improvement in major cardiovascular events (i.e., heart attacks, strokes, and deaths from those cases) in adults on weekly semaglutide who were overweight or obese (without diabetes) and with preexisting cardiovascular disease, as well as an improvement in all-cause mortality of 19%.

Quantifying the impact from the diabetic population requires a number of additional assumptions:

- **Prevalence of diabetes in the population** – The proportion of the population eligible for the drug as a diabetes treatment.
- **Effectiveness in diabetic population** – As per the non-diabetic model, but reflecting the lower effectiveness for weight loss in the diabetic population.
- **Uptake in diabetic population** – The proportion of eligible diabetics who are prescribed the treatments and start taking them. We allow for increases in uptake with future drug developments and price changes as per the non-diabetic methodology.
- **Relative risk of mortality and morbidity** – As per the non-diabetic model, but with benefits specific to the diabetic population.

Significant uncertainty surrounds these assumptions, particularly the assumptions regarding future uptake rate and the effectiveness and persistency of these medications.

² The morbidity impacts we model relate to what would typically qualify for a payment under a critical illness insurance benefit.

Table 4: Select assumptions affecting potential impact of incretin-based therapies

Assumption	Uncertainty	Materiality	Drivers of future improvements
Uptake	High	High	Improved access to drugs and lower costs
Persistency	Medium/ High	Medium	Improved cost, oral versions, and reduced side effects
Efficacy	Low/ Medium	High	Scope for new, more effective drugs

We address this uncertainty by running different scenarios to show the potential range of results.

When incorporating impacts from the various indications of incretin-based therapies, care should be taken to avoid double-counting. For example, obese diabetics are a special case and should not be given the full mortality and morbidity benefit for the weight-loss indication in addition to the diabetes indication.

The model quantifies mortality and morbidity improvements – by calendar year, sex, and age – directly attributed to the uptake of these medications for controlling weight in obese populations and for managing diabetes.

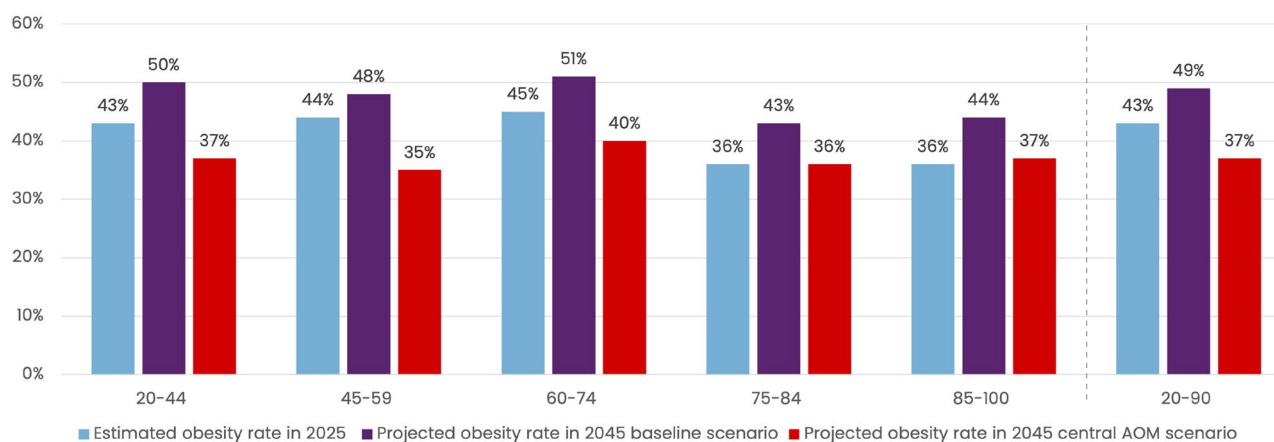
General population results

We built population models for four markets: The US, UK, Canada, and Hong Kong. Mortality and morbidity rates presented here apply on an attained-age basis, that is, they apply to the stated age band for the 20-year calendar period to 2045, and do not follow the cohort as it ages.

Obesity rates

RGA's obesity³ rate projections for the US non-diabetic population in 20 years (2045) are shown in Figure 3, both for our baseline scenario (without the medications) and our central scenario (with the medications).

Figure 3: US non-diabetic obesity rate projections for the year 2045



³ For the US, obesity is defined as a BMI of 30 or higher.

For ages 20–90, our model estimates an approximate reduction in obesity prevalence of about 12% for our central assumptions relative to the baseline scenario. The relative reductions in obesity rates are projected to be highest at younger ages, where uptake for the medications is expected to be higher. Across all ages, AOMs are projected to reverse the increasing obesity trend anticipated in our baseline (without AOMs) scenario, with most ages seeing projected obesity rates in 2045 lower than the estimated obesity rate in 2025.

Mortality rates

The following tables estimate the potential cumulative and annualized population improvements for mortality over the next 20 years. Our final model includes the combined impact of these drugs as weight-loss and diabetes treatments.

In addition to our central scenario, we also developed optimistic and pessimistic scenarios to understand the range of possible impacts under a reasonable range of assumptions and to reflect the inherent uncertainty. The optimistic scenario assumes:

- Higher weight-loss efficacy, based on emerging data from trials of AOMs
- Expanded access to the drug, driving higher uptake assumptions
- Higher persistency, driven by reduced costs and oral forms of the drug and fewer side effects
- Lower weight regain after stopping the drug
- Higher non-weight-loss-related mortality impacts

The pessimistic scenario, conversely, considers lower efficacy, lower uptake assumptions, higher and quicker weight regain, and lower non-weight-loss-related mortality impacts.

Table 5: Cumulative population mortality improvements over 20 years to 2045 due to AOMs under three scenarios

Market	Pessimistic	Central	Optimistic
US	1.0%	3.5%	8.8%
UK	0.5%	2.0%	5.3%
Canada	0.7%	2.6%	6.4%
Hong Kong	0.4%	1.4%	3.9%

Average across males and females, ages 20–90.

Table 6: Population annual mortality improvements due to AOMs under three scenarios

Market	Pessimistic	Central	Optimistic
US	0.05%	0.18%	0.46%
UK	0.03%	0.10%	0.27%
Canada	0.04%	0.13%	0.33%
Hong Kong	0.02%	0.07%	0.20%

Average across males and females, ages 20–90.

Impacts among markets differ due to factors including differences in the current obesity rates and future expected obesity trends, medication uptake (cost and eligibility), and the cause-of-death mix. For example, because Hong Kong has much lower current rates of obesity than the US and a lower proportion of deaths caused by CVD, the expected impact for Hong Kong is lower.

Mortality rates by age

The following tables indicate how potential cumulative and annualized population improvements for mortality in the central scenario are expected to differ by age.

Table 7: Cumulative population mortality improvement impacts over 20 years to 2045 due to AOMs by market and age

Age band	US	UK	Canada	Hong Kong
20-44	3.5%	3.1%	3.0%	2.1%
45-59	5.1%	4.2%	4.0%	2.1%
60-74	4.6%	3.1%	3.8%	1.6%
75-84	2.6%	1.2%	2.0%	1.2%
85-100	1.8%	0.9%	1.2%	0.8%
20-90	3.5%	2.0%	2.6%	1.4%

Central scenario, averaged across males and females.

Table 8: 20-year annualized population mortality improvement impacts of AOMs by market and age

Age band	US	UK	Canada	Hong Kong
20-44	0.2%	0.2%	0.2%	0.1%
45-59	0.3%	0.2%	0.2%	0.1%
60-74	0.2%	0.2%	0.2%	0.1%
75-84	0.1%	0.1%	0.1%	0.1%
85-100	0.1%	0.0%	0.1%	0.0%
20-90	0.2%	0.1%	0.1%	0.1%

Central scenario, averaged across males and females, and rounded to nearest 0.05%.

Differences in impacts by age are generally driven by differing levels of uptake expected by age (typically higher uptake in younger ages), as well as differences

in the cause-of-death profile by age. BMI is more strongly correlated with cardiovascular mortality vs. other causes of death; therefore, ages with higher cardiovascular mortality as a share of overall mortality are expected to see greater mortality reductions.

Morbidity rates

We define morbidity as the incidence of claims under a typical critical illness product. The following tables estimate the potential cumulative and annualized population improvements for morbidity over the next 20 years. Our final model includes the combined impact of these drugs as weight-loss and diabetes treatments.

Table 9: Cumulative population morbidity improvements over 20 years to 2045 due to AOMs under three scenarios

Market	Pessimistic	Central	Optimistic
US	0.6%	1.8%	5.0%
UK	0.3%	1.0%	2.9%
Canada	0.4%	1.5%	4.2%
Hong Kong	0.1%	0.4%	1.2%

Average across males and females, ages 20-90.

Table 10: Population annual morbidity improvements due to AOMs under three scenarios

Market	Pessimistic	Central	Optimistic
US	0.03%	0.09%	0.26%
UK	0.02%	0.05%	0.15%
Canada	0.02%	0.08%	0.21%
Hong Kong	0.01%	0.02%	0.06%

Average across males and females, ages 20-90.

Morbidity improvements are generally lower than mortality improvements due to a higher proportion of morbidity incidence (in a critical illness product) being caused by cancers (where the relative risks of incidence by BMI are lower), compared to mortality, with a higher proportion of deaths caused by CVD (where the relative risks by BMI are higher).

Insured and annuitant population considerations

The results described so far reflect potential changes to current mortality rates in the general population. There are several factors to consider when translating expected population improvements to insured life improvement assumptions:

- **Uptake** – The uptake of these medications among insured lives and annuitants is likely higher due to factors including out-of-pocket costs, health insurance coverage, and behavioral differences that support sustained lifestyle changes. Higher uptake in the insured and annuitant populations would generally lead to greater mortality and morbidity improvements, all else being equal.
- **Persistency** – Affordability and insurance coverage may be different in the insured population, leading to differences in drug adherence. Higher persistency would generally lead to greater mortality and morbidity improvements.
- **Obesity rates** – Obesity rates and future obesity trends typically differ among insured and annuitant populations compared with the general population. This can be driven by socioeconomic differences and – for insured lives – the selective effect of underwriting. In populations with lower levels of obesity and more moderate obesity trends, the projected mortality improvements would be lower.

Our model projects that the lower average BMI for insured groups has more of an impact than the increased ability to access the drugs, and so the overall mortality impact is typically lower for insured groups than for the general population.

Part 3. The everything drugs?

In Part 2, we examined how incretin-based treatments for obesity and diabetes could reshape future patterns of morbidity and mortality. Our central scenario reflected our current best-estimate assumptions for these indications, including expectations around future gains in efficacy, reductions in cost, and broader accessibility.

In this section, we examine how the impact of these treatments for obesity and diabetes could exceed those projected in our central scenario. We also consider the potential for further reductions in mortality and morbidity as the therapeutic landscape for incretin-based drugs expands beyond obesity and diabetes. A wave of regulatory approvals – particularly for cardiovascular disease – signals broader therapeutic potential, and growing optimism extends to their use in areas such as neurodegenerative disorders and addiction medicine.

Finally, we consider factors that could limit the impact of these therapies, outlining reasons why our expectations may not be fully realized.

Lowering cost to increase uptake

Growing competition and the arrival of generic and oral formulations are expected to lower costs significantly, which would widen access to these drugs. We already anticipate cost reduction in our uptake assumptions, but there is upside potential if uptake can be increased beyond our central scenario best-estimate assumptions. This is a fast-moving space, so it is important to frequently review assumptions.

To date, Novo Nordisk and Eli Lilly have dominated the incretin-based drug market. However, the landscape is shifting. A growing number of pharmaceutical and biotech companies are now developing novel therapies.

With 16 new drugs potentially launching in the next five years, it is anticipated that new challengers will account for roughly \$70 billion of the total incretin-based drug market, which is expected to [reach \\$200 billion by 2031](#).

Growing competition in GLP-1 drugs is expected to drive prices down over time, although the pace and extent of that decline will depend on several factors. As more companies enter the market, the increased supply and diversity of products are already putting downward pressure on prices.

In addition to competition among branded drugs, the arrival of generic versions and oral formulations – which are typically cheaper to manufacture – could further reduce costs. Analysts project that GLP-1 prices could decline by 10% annually by 2027, especially as insurers and pharmacy benefit managers negotiate deeper discounts and rebates.

Pricing is also shaped by regulatory policy, patent protections, and market exclusivity strategies. Wider provision of the drugs through government-sponsored healthcare services, such as Medicare and Medicaid in the US, would be expected to further increase uptake and persistency, especially if prices are materially reduced through negotiated discounts with the pharmaceutical industry. As more entrants bring new GLP-1 or multi-agonist drugs to market, the competitive pressure is likely to increase – potentially improving affordability and access for a broader patient population.

Novo Nordisk's Canadian patent for semaglutide expired in 2020 due to a missed maintenance fee. With no other semaglutide-related patents listed in Canada's Patent Register, the path is now clear for generic and biosimilar competitors to enter the Canadian market as early as January 2026, when regulatory data exclusivity also expires. Analysts expect prices to drop by 50%-80% once generics launch. Public health systems are also likely to pivot toward these lower-cost alternatives, increasing access for patients.

More-effective versions and oral formulations

The next wave of incretin and hormone-based therapies promises to offer advantages over the current generation. More-effective drugs could lead to greater weight loss and potentially greater mortality reduction. New formulations, such as oral drugs that are easier to take than injections or longer-lasting drugs that need to be taken less frequently, could increase uptake and adherence. Dramatically increased efficacy, uptake, and adherence could lead to positive upside impacts relative to our central scenario best-estimate assumptions.

Promising new candidates include:

- Amycretin (Novo Nordisk)
- Orforglipron (Eli Lilly)
- Survodutide (Boehringer Ingelheim)
- VK2735 (Viking Therapeutics)
- MariTide (Amgen)
- Retatrutide (Eli Lilly)

Among the most closely watched candidates is retatrutide, a triple-agonist developed by Eli Lilly that targets GLP-1, GIP, and glucagon receptors. In Phase II trials, retatrutide achieved up to 24.2% weight loss over 48 weeks, significantly outperforming existing therapies. This "triple-G" receptor approach may offer broader metabolic benefits, including improved energy expenditure and fat metabolism, although long-term safety and tolerability are still under investigation. Phase III trials are now underway, exploring its use not only for obesity but also for sleep apnea and osteoarthritis. Eli Lilly is expected to publish results in 2026.

Treatment indications continue to expand

The mechanisms underlying incretin-based therapies remain incompletely understood. Scientists know that GLP-1 and GIP receptor agonists help lower blood sugar, reduce appetite, and even protect the heart. But how do they do all of this? These drugs act on many parts of the body, not just the pancreas, and their effects go beyond what we would expect from just improving insulin release.

Incretin-based drugs are now being investigated – and in some cases approved – for a wide range of conditions, including cardiovascular disease, chronic kidney disease, sleep apnea, fatty liver disease (MASLD), neurodegenerative disorders, and even substance-use disorders. Following the results of the SELECT trial, the FDA approved a new indication for Wegovy (semaglutide) in March 2024: to reduce the risk of cardiovascular death, heart attack, and stroke in adults with cardiovascular disease and either obesity or overweight.⁴ If these indications continue to broaden and adoption scales accordingly, the cumulative impact on public health could be profound.

The growing approval pipeline could have significant implications for driving future improvements in morbidity and mortality, beyond areas discussed in Part 2. Looking ahead to late 2026, a wave of anticipated new therapeutic indications across a diverse range of clinical areas includes:

Indication	Drug (trial name)	Notes	Approval outlook
Type 1 diabetes (T1DM)	Tirzepatide (SURPASS-T1D-1)	<p>Incretin-based medications have traditionally been avoided in T1DM due to the risk of hypoglycemia and diabetic ketoacidosis (DKA). However, tirzepatide is being trialed in people with T1DM and obesity or overweight.</p> <p>Off-label use of GLP-1s in T1DM is increasing, especially in patients with insulin resistance or obesity.</p> <p>About 2 million Americans have T1DM</p>	<p>SURPASS-T1D-1 is a Phase III clinical trial expected to complete in May 2027.</p> <p>There are no official timelines for when it might be approved.</p>
Cardiovascular disease (CVD)	<p>Semaglutide (SELECT trial)</p> <p>Tirzepatide (SURMOUNT-MMO)</p>	<p>Multiple cardiovascular outcomes trials have been conducted or are ongoing.</p> <p>Previous trials such as SELECT showed cardiovascular benefit in people with obesity and CVD, but SURMOUNT-CVOT will test tirzepatide’s broader cardiometabolic effects and potentially support label expansion for primary prevention of CVD.</p> <p>Novo Nordisk and Eli Lilly are also hoping incretin-based drugs are approved for major adverse cardiovascular event reduction in adults with type 2 diabetes.</p> <p>Almost 130 million Americans have had some form of CVD between 2017 and 2020.</p>	<p>Semaglutide was approved by the FDA in March 2024. This approval was based on the SELECT trial.</p> <p>SURMOUNT-MMO is a Phase III clinical trial expected to complete in October 2027. FDA approval could follow shortly after, depending on the trial results and regulatory review timelines.</p>

⁴Defined as a BMI in the range 25–30 in the US, Canada, and UK, or 23–25 in Hong Kong.

Indication	Drug (trial name)	Notes	Approval outlook
Heart failure with preserved ejection fraction (HFpEF)	Semaglutide (STEP-HFpEF)	The drugs are actively being evaluated for this indication, and approval may be on the horizon.	The drugs have not yet been approved by the FDA.
	Tirzepatide (SUMMIT)	As of 2025, approximately 6.7 million American adults are living with HF. Approximately 1 in 4 persons will develop HF in their lifetime.	Novo Nordisk is hoping for approval soon (possibly second half of 2025). Recent Phase III data for tirzepatide showed a 38% reduction in adverse heart failure outcomes compared to placebo.
Peripheral artery disease (PAD)	Semaglutide (STRIDE)	Semaglutide is being trialed in patients with symptomatic PAD who also have type 2 diabetes. Between 21 and 26 million Americans are living with PAD.	Semaglutide for PAD is expected to receive FDA consideration in the first half of 2026.
Obstructive sleep apnea (OSA)	Tirzepatide (SURMOUNT-OSA)	Tirzepatide is the first-ever pharmacological treatment for OSA, which has traditionally relied on devices like CPAP.	Tirzepatide was approved by the FDA in December 2024 for treating moderate-to-severe OSA in adults with obesity.
	Mazdutide (GLORY-OSA)	Mazdutide and orforglipron are in earlier phases of development for similar indications.	Other GLP-1 drugs may follow, pending results from ongoing trials and regulatory submissions.
	Orforglipron (ATTAIN-OSA)	As of 2024, around 80 million US adults aged 20 and older (almost 1/3 of the adult population) are living with OSA, making it one of the most prevalent chronic conditions in the country.	
Metabolic dysfunction-associated steatohepatitis (MASH)	Semaglutide (ESSENCE)	Recent FDA approval for this indication marks a significant shift in hepatology, integrating liver disease into broader metabolic care. It also supports early intervention strategies targeting metabolic dysfunction before cirrhosis develops.	As of August 2025, the FDA has approved semaglutide for the treatment of MASH in adults with moderate-to-advanced liver fibrosis, excluding cirrhosis. Full approval for semaglutide in MASH depends on long-term outcomes from the ESSENCE trial, expected by 2029.
	Tirzepatide (SYNERGY-NASH)	MASH affects approximately 15 million US adults.	Tirzepatide is currently not approved for MASH, but the SYNERGY-NASH Phase II trial results are considered highly promising. Phase III trials are expected to start soon. Other incretin-based drugs are also in trial stage.

Indication	Drug (trial name)	Notes	Approval outlook
Chronic kidney disease (CKD)	Semaglutide (FLOW) Tirzepatide (TREASURE-CKD)	The drugs are seen as a breakthrough in the treatment of CKD, particularly in patients with type 2 diabetes and/or obesity. More than 1 in 7 US adults – an estimated 35.5 million people – are living with CKD.	Based on the FLOW trial results, semaglutide was approved in January 2025 to reduce the risk of CKD progression, kidney failure, and cardiovascular death in adults with type 2 diabetes and CKD. Eli Lilly's TREASURE-CKD Phase II trial is expected to complete in October 2026.
Osteoarthritis (OA)	Semaglutide (STEP-9)	The drugs may help with OA through weight loss (reducing joint load), anti-inflammatory effects in joint tissues, and improved metabolic profile, which may slow OA progression. More than 32.5 million US adults are affected by osteoarthritis, making it the most common form of arthritis and a leading cause of disability.	The drugs are not yet approved for OA treatment. The STEP-9 trial showed strong symptomatic relief, but structural disease modification is still under investigation. Regulatory recognition of OA as a weight-related comorbidity could expand access.
Alzheimer's disease (AD)	Oral semaglutide (EVOKE and EVOKE+) Liraglutide (ELAD)	Clinical trials and observational studies suggest the drugs may offer neuroprotective effects (reduce neuroinflammation, insulin resistance, and amyloid/tau toxicity) and slow cognitive decline. As of 2025, an estimated 7.2 million Americans aged 65 and older are living with AD.	Semaglutide could be submitted for FDA review after EVOKE trial results in late 2025. (Approval could then follow in 2026). Liraglutide shows promise but lacks Phase III data
Addiction, including alcohol use disorder (AUD)	Semaglutide (NCT05520775) Tirzepatide (DUALPSYCHIATRY)	There is some evidence that the drugs can reduce craving and drinking outcomes, justifying larger clinical trials to evaluate GLP-IRAs for AUD. Further, researchers are looking to provide evidence from real-world data that the drugs could be used to treat stimulant-use disorder and/or opioid-use disorder (OUD). Tirzepatide and semaglutide have been tested in Phase II trials to treat patients with AUD. Off-label use is growing, especially in patients with obesity or diabetes.	No FDA approval yet for addiction treatment. Experts suggest it could be at least five years before potential approval.

Potential role as preventive medicines

As incretin-based therapies continue to demonstrate a wide range of health benefits, interest is growing in their potential role as preventive medicines. Their systemic anti-inflammatory effects, metabolic regulation, and influence on satiety and insulin sensitivity suggest they could help prevent the onset of multiple chronic conditions – especially in high-risk populations.

The shift from treatment to prevention could mark a paradigm change in how we approach metabolic and age-related diseases. GLP-1 therapies have already shown efficacy in reducing major adverse cardiovascular events and slowing kidney disease progression in people with diabetes and obesity. If these benefits extend to individuals without established disease, we could see a significant reduction in morbidity and mortality across the general population.

Uncertainties, risks, and limitations

The central scenario results set out in Part 2 are based on current best-estimate assumptions for these drugs being used to treat diabetes and weight-loss indications only. In Part 3, we outlined reasons for optimism that the impacts of incretin-based therapies could exceed those assumed in our central scenario – largely due to their emerging use in treating a broader range of diseases, and potentially even in disease prevention. We may also see greater impacts from these therapies within their current indications (in line with our optimistic scenario) if newer versions prove to be more cost-effective than expected and/or deliver enhanced clinical performance. This could include increased efficacy, fewer side effects, improved tolerability, and more personalized treatment options.

The upside potential of these drugs is exciting, but it is important to recognize challenges that must be overcome to fully achieve anticipated impacts.

We have discussed challenges linked to safety, side effects, access, adherence, and affordability in this report.

In addition, the legal landscape surrounding incretin-based therapies is complex. In the US, for example, manufacturers have faced multidistrict litigation over alleged links to pancreatic cancer, with plaintiffs claiming inadequate warnings and defective design. Although courts have largely ruled in favor of the defendants – citing lack of causation and federal pre-emption of state-law claims – the litigation has highlighted the challenges of pharmacovigilance and the burden of proof in drug safety cases. Additionally, the rise of compounded versions of GLP-1 drugs during shortages has introduced new liability risks, particularly around quality control and off-label marketing.

To the extent these challenges cannot be overcome, risk remains that AOM impacts could be lower than we have assumed and potentially more in line with our pessimistic scenario.

Part 4. Implications for insurers

Insurers should consider the impact of AOMs across their business:

- Assess how AOMs may impact protection, morbidity, and longevity experience
- Review trend assumptions to identify whether changes are needed
- Establish processes to keep on top of this fast-moving space
- Consider new lapse risks
- Assess how AOMs might affect underwriting and claims

Insured impacts and reviewing trend assumptions

Insurers should consider adjustments to their specific mortality and morbidity improvement assumptions to reflect AOMs. Accounting for specific drivers in future improvement projections is fraught with difficulties and requires a careful blend of analysis and judgment.

[“Evaluating Biometric Trend Drivers: How to reflect medical breakthroughs and other drivers in forward-looking assumptions”](#) explores the practicalities of how to maintain an up-to-date view on emerging drivers such as AOMs and provides a framework for incorporating insured impacts into insured improvement bases.

The impact on insureds and annuitants reflects the characteristics of the insured book. To explore insured impacts further, and how they may translate to your policyholders, reach out to your local RGA representative.

New lapse risks

The use of AOMs introduces the risk of anti-selective policyholder behavior, as individuals who have lost considerable weight may lapse their rated policies and re-enter with better terms. As such, insurers may not capture the full economic benefit of improved mortality and morbidity.

Insurers will need to consider how this anti-selection risk may affect their lapse assumptions.

Underwriting and claims considerations

Underwriting

The increasing use of incretin-based therapies promises to significantly influence underwriting risk assessment, illustrating the need for underwriting practices to evolve alongside medical innovation. Despite experiencing metabolic and cardiovascular improvements, many individuals will retain underlying conditions such as diabetes, hypertension, dyslipidemia, sleep apnea, or fatty liver disease (MASLD). Underwriters therefore need to continue to review and assess medical evidence for any associated side effects and potential comorbidities, including cardiovascular status, renal and hepatic function, and mental health or cognitive concerns.

People who have experienced medication-driven weight loss present new underwriting risks. The weight gain that occurs if treatment is stopped may be dramatic compared to what might be expected from individuals not taking the medication, with concomitant increases in mortality and morbidity risk throughout the duration of the policy. Weight at underwriting

might also mask accumulated harms and previous high-risk weight status. Addressing these issues will require insurers to consider an applicant's BMI history rather than simply BMI at the time of application. Applicants with well-documented, physician-monitored AOM use and stable clinical parameters may present a favorable risk profile, especially compared with untreated obese or diabetic individuals. However, the line between medical therapy and lifestyle enhancement becomes increasingly blurred. As more healthy individuals seek AOM prescriptions for cosmetic or preventive reasons, insurers must consider how to interpret such use in underwriting and build an understanding of the nuanced, evolving interplay among pharmacologic intervention, lifestyle behaviors, and long-term outcomes.

As evidence accumulates, underwriting approaches must evolve to recognize improvements while maintaining vigilance in validating these therapies' potential long-term and sustainable mortality and morbidity gains. Furthermore, the continuing education of underwriters to ensure accurate interpretation of disclosures and evidence, including risk markers and polypharmacy, is essential.

Claims

Understanding weight trends, clinical indications for AOMs, remaining comorbidities, and any treatment side effects are all important factors to consider as part of claims management practices. As with other material medical conditions, accurate disclosures at the underwriting stage may need to be validated at claims time. Claims assessors will need a deep understanding of the use of AOMs to ensure accurate interpretation of information in relation to disclosures made as part of the insurance application.

In the nearer term, disability income claimants with sustained weight loss could demonstrate an increase

in functional capacity, including the ability to return to work. Again, considering remaining comorbidities and side effects will be essential as they could still impact function even after weight loss.

A potential longer-term impact may be a change in claims cause trends for critical illness claims. For example, a valid claim for end-stage diseases that currently rely on metabolic markers may be delayed as a result of improved clinical status with the use of AOMs. Critical illness definitions may need to be future-proofed to align with these medical advances.

Health insurers need to consider the potential impact of multiple aspects, including benefits and coverage and cost implications and controls. They should also play a role in ensuring that AOMs are used responsibly and in establishing benefit sustainability.

Conclusion

AOMs have the potential to significantly improve population mortality and disease incidence rates.

The impact on insured groups is likely to be lower, and it may be too early to make material adjustments to insured trend assumptions, but the efficacy of AOMs to date increases confidence in future mortality and morbidity improvements.

This is a fast-moving space with significant uncertainties, so monitoring developments closely will be vital to responsible and successful insurance practices. Model assumptions will need continual refining as new evidence emerges and as new indications for incretin and hormone-based medications are approved.

To explore insured impacts further, and how they may translate to your policyholders, reach out to your local RGA representative.

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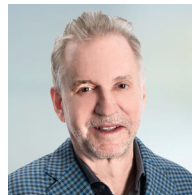
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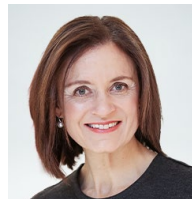
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