

FOUNDER REPORT

When Biology Crosses Categories Before Medicine Does

Why evidence architecture matters when medicines
cross organs, specialties, and labels

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In brief. A drug's biology often reaches across organs and specialties years before the evidence system — labels, guidelines, practice — catches up. That lag is not a failure of intelligence; it is how clinical evidence is built: one disease, one endpoint, one specialty at a time. This report traces where the gap has been real, where it closed fast, where it took decades, and where the pattern does not hold — all of it a question of **evidence architecture**: the alignment of mechanisms, trial populations, endpoints, labels, and guidelines that determines what a development program can actually see.

Where this fits

Part of our metabolic-integration series. This founder report states the broader principle: biology can outrun the categories medicine uses to prove, label, and adopt it. It is anchored in metabolic medicine but uses cases across therapeutic areas to show when the pattern holds — and when it does not. It is the middle piece of three: the Founder Essay, [The Translational Gap in Metabolic Disease](#), introduces the problem in narrative form, and the Strategy Report, [Metabolism as Platform Medicine](#), applies the same lens to the decisions a metabolic program faces.

A glucose drug that became a heart-failure drug

SGLT2 inhibitors were designed to lower blood sugar by making the kidney excrete glucose. They entered development as a glucose-lowering diabetes idea. Then a trial built to check their cardiovascular *safety* — **EMPA-REG OUTCOME** — found something its designers were not looking for: fewer cardiovascular deaths and fewer heart-failure hospitalizations, on a timescale and scale that glucose-lowering alone could not explain.^[1]

The natural next question was whether the heart-failure benefit was really about the heart, not the diabetes. A dedicated trial, **DAPA-HF**, answered it: an SGLT2 inhibitor reduced heart-failure events in patients **with and without** diabetes.^[2] Within a few years, SGLT2 inhibitors moved from "diabetes drugs" to guideline-recommended heart-failure therapy.^[3]

Read forward, that story looks inevitable. Read at the time, it was not. The biology that made these drugs matter for the heart was present from the start; the evidence that revealed it arrived years later, and only because a trial happened to be pointed in the right direction. That ordering — biology first, recognition later — is the subject of this report.

Exhibit 1 places that sequence beside two other classes — beta-blockers and GLP-1 receptor agonists — where the same early-signal-to-proof-to-recognition path unfolds over spans ranging from a few years to about two decades.

EXHIBIT 1 · INTEGRAL BIOSTRATEGY

Signal → proof → recognition, across three drug classes

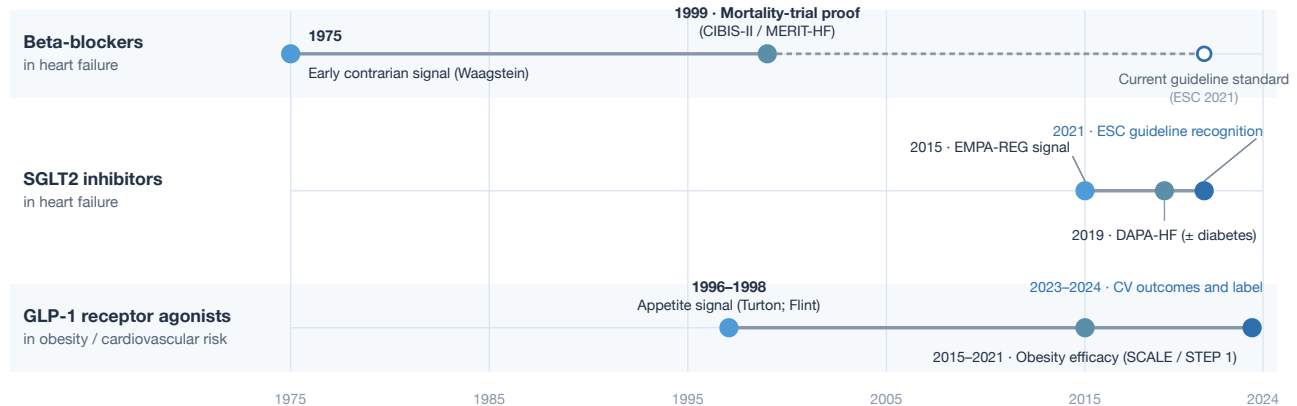
Biology can become legible years before the evidence system is ready to act — and the path to recognition differs by class.

● Early signal

● Trial proof

● Recognition / guideline

○ Current standard (secondary)



Milestone dates are documented from the report's cited sources (Waagstein 1975; CIBIS-II / MERIT-HF 1999; ESC 2021; EMPA-REG 2015; DAPA-HF 2019; Turton 1996 / Flint 1998; SCALE 2015 / STEP 1 2021; SELECT 2023; FDA Wegovy CV label 2024).

Spans are illustrative and depend on anchor choice; they are not universal lag estimates.

The broader pattern

Across many therapeutic classes, the same shape recurs: **the biology crosses a category boundary before the systems that certify medicines do**. A mechanism turns out to matter in an organ, a specialty, or a disease label different from the one it was first approved for. The science is legible — sometimes for years — before anyone builds the trial, writes the label, updates the guideline, or redirects development effort.

It helps to separate two moments. There is the moment a broader **signal** becomes biologically credible — a receptor mapped in a new tissue, an unexpected effect in a secondary endpoint, a mechanistic argument that a drug should do more than its label says. And there is the later moment the field takes **action** — a dedicated trial, an approval, a guideline change. The interval between those two moments is where the interesting questions live. It is sometimes short, sometimes a generation long, and the difference is rarely about how good the science was.

Clinical medicine itself has started to acknowledge that disease categories blur. The recent framing of "cardiovascular-kidney-metabolic" health is an explicit recognition that conditions long managed in separate clinics are, in substantial part, one connected biology expressed in different tissues.^[4] The drugs in this report are early, concrete instances of that idea.

Why evidence systems lag biology

The lag is structural. Three features do most of the work.

You only see what you measure. A trial is, in effect, a lens. A diabetes trial measures HbA1c; it can prove glucose control and almost nothing else. A hypertension trial measures blood pressure. If a drug's broader benefit lands on an endpoint the trial was never built to capture, the trial cannot see it — no matter how real the biology is. SGLT2 inhibitors' heart-failure benefit surfaced only when a *different* kind of trial, one built around cardiovascular endpoints,

was run; no improvement to the diabetes trials would have revealed it. Endpoint choice is not a technical detail; it decides what is knowable.

Specialties are siloed. A drug developed in one therapeutic area carries the identity of that area. When it shows a signal in another organ, it has to be "handed off" to a different specialty, with its own meetings, budgets, trial networks, and prescribers. Real-world adoption shows the friction: a drug can be enthusiastically prescribed by the specialists who own its original indication and barely touched by the specialists who own the new one, long after the evidence is in. Identity travels more slowly than evidence.

Paradigms lock in. Sometimes the broader use doesn't just cross a boundary; it overturns a settled mechanistic story. When that happens, the evidence has to dislodge a belief before it can change practice, and beliefs are sticky. This is the most expensive form of the lag, and we return to it below.

None of these is irrational. Each made the evidence system trustworthy for the questions it was built to answer. Together, they mean that broad biology can sit in plain sight, in the published literature, while the apparatus that turns biology into approved practice looks the other way.

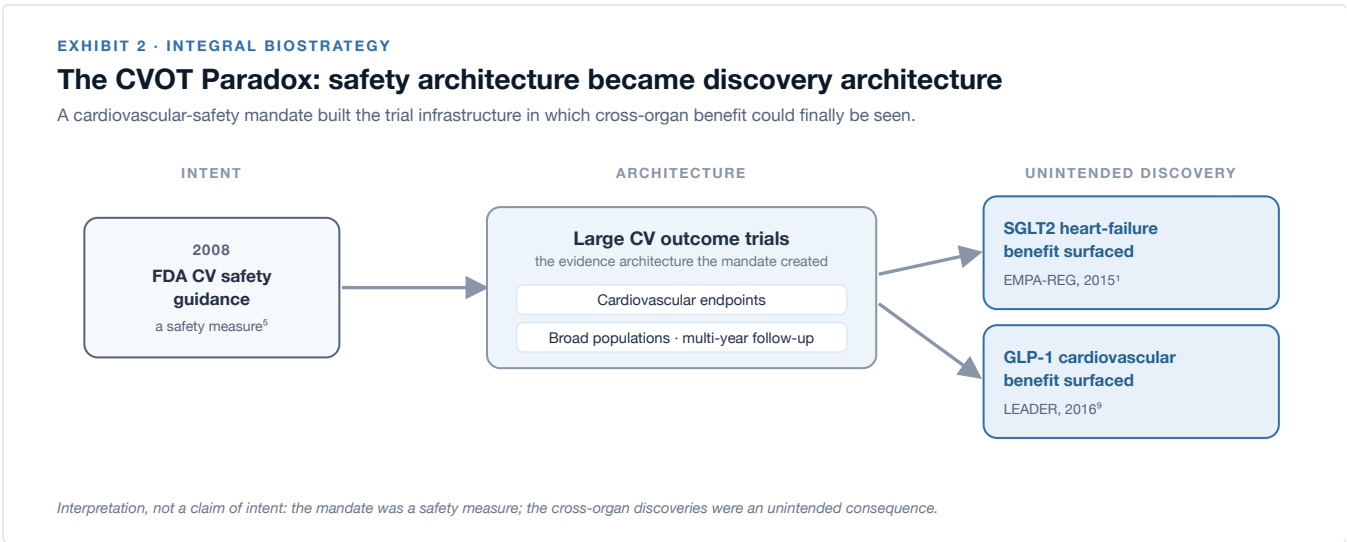
The accidental experiment: CVOTs and the evidence architecture they created

That scaffolding — the trials, endpoints, populations, and timelines a field has in motion — is what determines which questions can be answered at all. Change the scaffolding and you change what becomes visible.

There is a clean, almost accidental, demonstration of this. After safety concerns about an earlier diabetes drug, the FDA issued guidance in 2008 requiring new type-2-diabetes therapies to be evaluated for cardiovascular safety.^[5] The intent was defensive — make sure these drugs did not raise cardiovascular risk. The effect was something else entirely. To meet the requirement, companies had to run large trials with cardiovascular endpoints in broad populations followed over years. That is exactly the architecture in which a cross-organ benefit could finally be seen.

It was in those mandated cardiovascular trials that SGLT2 inhibitors revealed their heart-failure benefit,^[1] and GLP-1 receptor agonists revealed cardiovascular benefit.^[9] A safety requirement, created for an unrelated reason, became the instrument that surfaced biology the field had not been looking for.

The sequence is worth seeing whole (Exhibit 2): a defensive safety mandate built the very architecture in which cross-organ benefit could surface.



We offer this as an interpretation, not a claim about anyone's intent: no one designed the 2008 mandate to discover platform biology, and it would be wrong to say these benefits could *never* have been found another way. But the

sequence is instructive. The rate-limiting step was not the science and not the molecules. It was whether a trial existed that could see the answer. When the architecture changed, recognition followed.

When the model changes: beta-blockers and paradigm reversal

The longest lags happen when broader biology requires overturning an established mechanistic model.

For most of the twentieth century, beta-blockers were considered inadvisable — at times contraindicated — in heart failure. The reasoning was coherent: beta-blockers reduce the force of cardiac contraction, and a failing heart was thought to need all the contractile force it had. A Swedish group reported, as early as the mid-1970s, that patients with a failing, dilated heart could actually improve on beta-blockade.^[12] The finding ran against the prevailing model and was met with skepticism.

What eventually changed practice was a new *theory*: a neurohormonal model in which chronic sympathetic activation is itself toxic to the failing heart, and then the trials that tested it. **CIBIS-II** and **MERIT-HF** showed that selected beta-blockers reduced mortality in heart failure,^{[13][14]} and guidelines have since made them a standard part of therapy.^[3]

From first contrarian signal to guideline adoption was roughly two decades. The delay was not caused by weak data or absent molecules; the molecules existed the whole time. It was caused by a mechanistic belief that had to be replaced before the evidence could be heard. When recognition requires a paradigm to change, expect the gap to be measured in decades, not years.

When recognition accelerates: GLP-1 and a learned evidence system

The opposite can also happen: once a field has seen a pattern, it acts on the next instance far faster.

GLP-1 receptor agonists began as glucose-lowering drugs for type-2 diabetes. Their *appetite* biology — the basis of their later use in obesity — became credible in stages: GLP-1 was shown to reduce feeding in rodents in the mid-1990s,^[6] and to suppress appetite and food intake in humans by the late 1990s.^[7] (One date is often blurred. The 1986–87 work established GLP-1's *insulinotropic*, incretin biology — its effect on insulin secretion, not appetite. The appetite signal came roughly a decade later.) Obesity efficacy was then established clinically with liraglutide and, more dramatically, semaglutide.^{[8][7a]}

The *time from new evidence to action* then shortened as the field gained confidence in the class. The earliest cross-organ steps took years to move from trial to label. By the time a cardiovascular outcomes trial — **SELECT** — showed that semaglutide reduced major cardiovascular events by about 20% in people with overweight or obesity and established heart disease but **without** diabetes,^[10] the regulatory response was comparatively quick: the FDA expanded the label to include cardiovascular risk reduction in 2024.^[11]

We will resist putting a precise multiplier on that acceleration; the exact intervals depend on which milestones you anchor to. The qualitative point still holds, and it is the useful one: a system that has already learned to recognize a class's broader biology acts on the next signal faster. Recognition is not a fixed property of the science; it is partly a property of the system's prior experience.

When the pattern does not apply

A pattern that explains everything explains nothing. The cases above are real, but the more useful discipline is knowing where this way of thinking **fails**. Three boundaries matter.

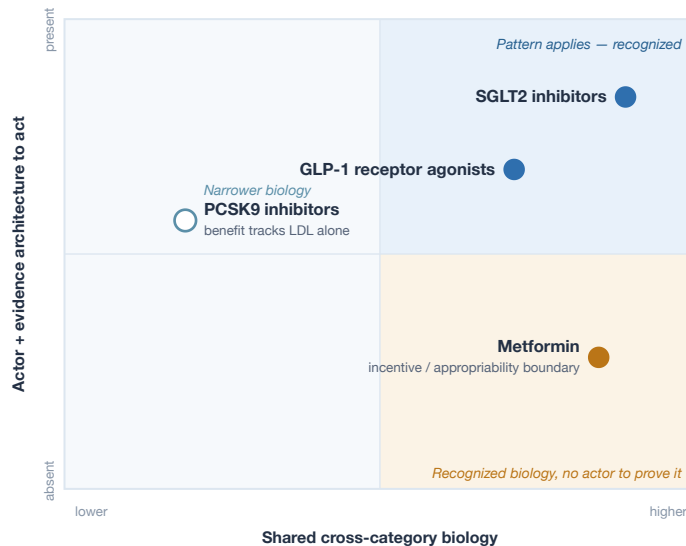
Exhibit 3 maps both sides of that line — the cases where the pattern applies, and the three ways it does not.

EXHIBIT 3 • INTEGRAL BIOSTRATEGY

When the pattern applies — and when it does not

Not every broader biological signal becomes a strategy. Two conditions must hold at once.

● Pattern applies ● Actor / incentive boundary ○ Narrower biology



Insulin — outside the frame

The broader biology is recognized, but the mechanism cannot reach the target — so the two axes do not apply. A special case, not a quadrant.

Positions are illustrative judgments, not scores. The matrix is a boundary map, not a therapeutic recommendation.

Sources: SGLT2^{1,2,3} · GLP-1^{6,7,8,9,10,11} · PCSK9¹⁸ · metformin^{19,20} · insulin²¹.

No broader biology there at all. Not every effective drug in a given risk pathway carries a cross-category story. Statins are the classic example of pleiotropy: beyond lowering cholesterol, they appear to reduce vascular inflammation, and a trial in people with normal cholesterol but elevated inflammatory markers (high CRP) showed they still reduced cardiovascular events.^[16] A later trial that targeted inflammation directly, without lowering cholesterol, also reduced events — evidence that inflammation is a causal pathway, not just a marker.^[17] But PCSK9 inhibitors — extraordinarily powerful cholesterol-lowering drugs — do **not** reproduce this broad inflammatory biology; their benefit tracks the degree of LDL reduction.^[18] PCSK9 inhibitors are not a failure; they are highly effective at what they do. They are a reminder that two drugs acting in the same risk pathway can have very different *breadth* of biology. The cross-category story is mechanism-specific, not a property you can assume.

Recognition without an actor who can move on it. Metformin has decades of signals suggesting benefits beyond glucose control, including in the original studies of overweight patients with type-2 diabetes.^[19] When metformin was finally tested in a large breast-cancer trial, it did not improve disease-free survival.^[20] It has also been generic for decades, so no sponsor has the exclusivity or incentive to fund the large trials a new indication would require. This is an **incentive and appropriability** boundary, not a story of value waiting to be unlocked. Where no actor has both the capability and the incentive to act, the absence of action is market structure, not missed recognition. It should not be dressed up as the latter.

The mechanism cannot reach the target. Some broader biology is recognized but pharmacologically out of reach. Insulin treats insulin deficiency, but it does not correct the cellular insulin *resistance* that drives type-2 disease; a large trial of basal insulin found neutral cardiovascular outcomes.^[21] Recognizing a broader role does not help when the drug's mechanism is mismatched to it.

Holding these boundaries in view is what separates a useful lens from a story that flatters every drug. The honest version of this idea must be able to name its own failure cases.

What this means for teams building or evaluating medicines

If the gap between biology and recognition is largely structural, then it is partly *designable*. A few practical implications follow — offered as questions to ask, not as a formula.

Exhibit 4 reads the six cases side by side; across very different stories, the column that does the work is the same one — the evidence architecture.

EXHIBIT 4 · INTEGRAL BIOSTRATEGY

Evidence architecture decides what can be seen

Each case illustrates a different recognition — or boundary — logic. Read across: the highlighted middle column is the point.

● Recognized ● Actor / incentive boundary ○ Narrower or mechanism boundary

Case	Original frame	Broader signal or question	Evidence architecture	Action / boundary	Lesson
● SGLT2 inhibitors	Glucose-lowering for type-2 diabetes	Heart-failure and renal benefit beyond glucose	A mandated CV outcomes trial saw it; a dedicated HF trial confirmed it (with / without diabetes)	Guideline-recommended heart-failure therapy	The right trial endpoints made the biology visible
● Beta-blockers	Implausible — even contraindicated — in HF	Chronic sympathetic drive harms the failing heart	A new neurohormonal model, then mortality trials	Paradigm reversal → standard therapy	When biology contradicts the model, recognition takes decades
● GLP-1 receptor agonists	Glucose-lowering incretin for diabetes	Appetite and obesity, then cardiovascular risk	Appetite signal early; a CV outcomes trial much later	Obesity and CV-risk labels; action accelerates	A learned evidence system acts on the next signal faster
○ PCSK9 inhibitors	Potent LDL-cholesterol lowering	Does it share statins' broader biology?	Outcome trial: benefit tracks the degree of LDL lowering	Effective; narrower biology	Same risk pathway ≠ same breadth of biology
● Metformin	Generic biguanide for diabetes	Decades of broader signals (including cancer)	Few sponsors or incentives for large trials; one ran in breast cancer — negative	Incentive / appropriability boundary	Recognition needs an actor able to prove it
○ Insulin	Replacement for insulin deficiency	Could it address insulin resistance or CV risk?	Basal-insulin outcome trial: neutral CV outcomes	Mechanism cannot reach the target	Recognized biology still needs a mechanism that fits

Rows summarize cited evidence in the studied populations. This is a recognition map, not a therapeutic recommendation or a scoring system.

Sources by row: SGLT2 — EMPA-REG, DAPA-HF, ESC 2021; beta-blockers — Waagstein, CIBIS-II / MERIT-HF; GLP-1 — Turton / Flint, SCALE / STEP 1, SELECT, FDA label; PCSK9 — FOURIER (vs JUPITER / CANTOS); metformin — UKPDS

Decide early what your evidence can ever see. The endpoints, populations, and trials you choose at the start determine which biology you will be able to demonstrate later. If a drug's mechanism plausibly reaches beyond its lead indication, the cheapest time to make that visible is before the pivotal program is locked — not after. You cannot retrofit an endpoint into a trial that has already read out.

Read the biology across categories, not within a specialty. The most consequential signals in the cases above crossed organ boundaries: a kidney drug that helped the heart, a diabetes drug that worked on appetite. A review that only asks "is this a good [original-indication] drug?" will miss them by construction.

Separate the signal from the conditions for acting on it. A strong biological signal is necessary but not sufficient. Ask, honestly: is there a credible mechanism shared across the categories? Is there an actor with the exclusivity and capability to run the proof? Does the regulatory and trial architecture exist to capture it? Where the answer to any of these is no — as with metformin, or insulin, or PCSK9's missing pleiotropy — the right move is to say so, not to narrate value that cannot be realized.

Treat boundary cases as information, not inconvenience. The failures are where the real knowledge is. A program that can articulate where its broader thesis would *break* is more credible, and better governed, than one that cannot.

The question is rarely whether a molecule could have a bigger story; it is whether the biology, incentives, and evidence architecture are aligned enough for that story to become provable.

That framing leads to a more disciplined set of questions:

- Does the mechanism plausibly cross organs, diseases, or specialties?

- Are the current endpoints capable of detecting that biology?
- Is there an actor with the incentive and capability to prove the broader use?
- Is the thesis mechanism-specific, or merely extrapolated from a class or pathway?
- Would the next study be capable of changing labels, guidelines, reimbursement, or prescribing behavior?

None of this requires predicting the future, and none of it should be sold as a crystal ball. The strategic task is not to predict every future indication. It is to build evidence architecture that can see what biology is already beginning to show — and to know when the pattern does not apply.

Evidence notes and limitations

This report is a measured synthesis of well-documented cases, written for discussion. A few honest caveats:

- The cases here were chosen because they illustrate the pattern (and its boundaries). They are not a representative sample of all drugs, and they cannot, by themselves, tell you how *often* broad biology goes unrecognized. Drugs whose broader biology was pursued and found nothing — and drugs that never reached the literature — are under-represented in any such selection.
 - Timelines from "signal" to "action" depend on which milestones you anchor to; reasonable people will date them differently, which is why this report avoids precise single-number lags.
 - Where a benefit is described, it reflects the cited trial's reported result in its studied population; it is not a recommendation, and it is not a claim that the result generalizes beyond that population.
 - The most recent trials are cited from current primary sources; as with any analytical report, every reference should be checked at final copy-edit before external use.
 - This is an analytical essay, not a peer-reviewed study, and it is not offered as one.
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All references below are primary trials, regulatory documents, society guidelines, or peer-reviewed reviews. Verify each DOI/PMID at final copy-edit before external use.

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