

The bumpy road to evidence: why many research findings are lost in translation

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We have come a long way

When, more than 2500 years ago, Thales of Milet (624–547 BC) claimed that nature was ruled by laws and not by gods, he changed the world.¹ Such a concept allowed for the discovery and mathematical proof of impersonal causation of what, until then, had been a mystery ruled by unpredictable gods. Indeed, ever since then the understanding of nature—today we would call it the natural sciences—has become a major activity of mankind. With this strategy, we have come a long way. Initially, it allowed us to use the position of stars and planetary motion for navigation and the discovery of new continents; next, it set the basis for the development of engines and technologies; and finally, it led to the discovery of the human body. Eventually, this allowed for the rise of modern medicine, among many other achievements.

As a consequence, theology and philosophy, the dominant disciplines of ancient times, were increasingly challenged and, to a great extent, replaced by scientifically based knowledge about the world, about nature, mankind, and disease. Such knowledge produced practically useful consequences, such as pumps, steam, and later, petrol-driven engines, trains, cars, aeroplanes, and rockets, allowing us to fly to New York or to the moon. In life sciences, it brought about hygiene, anaesthesia, and in turn, aseptic surgery, antibiotics, vaccination, resuscitation, cardiac surgery, and interventional cardiology;^{2,3} an impressive and unanticipated achievement indeed.

What is evidence?

What is evidence? At the beginning of any discovery stands an individual with curiosity; an initial observation is the first step in the process. When Columbus sat at the beach—as the famous movie by Ridley Scott leads us to believe—watching ships leaving the harbour with his son Diego, he asked him, 'Look!'

'Half of the ship has gone', replied Diego.

'And now?'

'It's gone.'

'What does it tell you?'

Diego was not sure.

'It is round', replied his father, 'like this', presenting an orange he was about to eat.

Thus, the interpretation of a finding is as important as the observation itself. But that is not enough; it needs proof, i.e. the journey to the West and the persistence to pursue it. Columbus did it all and discovered a new continent, now known as the Americas.

What is a scientific fact? Above all, it should be provable, i.e. confirmed or falsified by one's own data and those of other scientists. And indeed, most scientists spend their day providing data to confirm their conclusion. Karl Popper (1902–94) taught us that this is not it.^{4,5} In fact, observations have to survive the proof of time; the scientific process develops along conjectures and refutations. The statement that all swans are white was falsified with the discovery of black swans in Australia.^{6,7} Another important aspect of discovery is the fact that it always evolves within a paradigm,⁸ i.e. in medicine, a basic concept of what the major causes and mechanisms of a disease are. Importantly for what is discussed below, by sheer probability new claims are more likely to be falsified; thus, the road to evidence is, by design, a bumpy one.

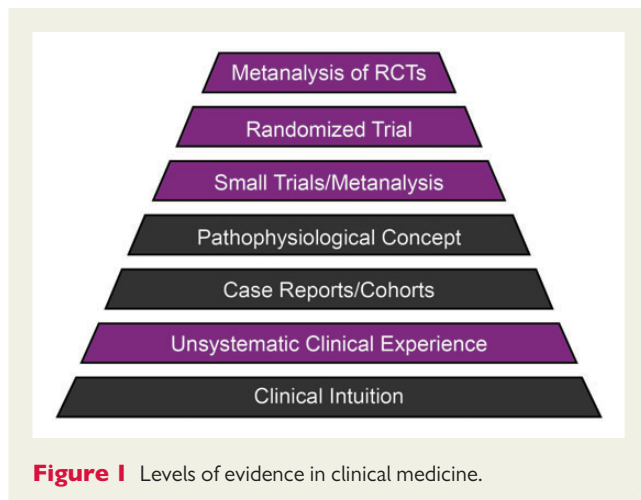
And indeed, innovations are difficult to predict. Simon Newcomb (1835–1909), a physicist of the 19th century, said: 'Flying with machines that are heavier than air is without practical importance and senseless, if not completely impossible.' Yet today, about 3 billion passengers travel by air each year. Around the same time, the famous surgeon Theodor Billroth said: 'That surgeon who ever would attempt to sew a wound of the heart can be sure of losing any respect of his colleagues for ever.' Yet today, more than a million cardiac operations are performed every year, not to mention catheter interventions.

Particularly in an applied science such as medicine, the practical consequences of a theory are as important as the fact that it has stood the test of time. Indeed, Anitchkow's seminal observation in rabbits fed a high-fat diet led to the concept that fat or its components will lead to atherosclerosis and its complications, such as myocardial infarction and stroke.⁹ The Framingham study prospectively studied this relationship and found an association also in humans.¹⁰ However, only the discovery of 3-hydroxy-3-methyl-glutaryl-coenzyme A inhibitors, the statins, enabled studies that eventually proved a causal

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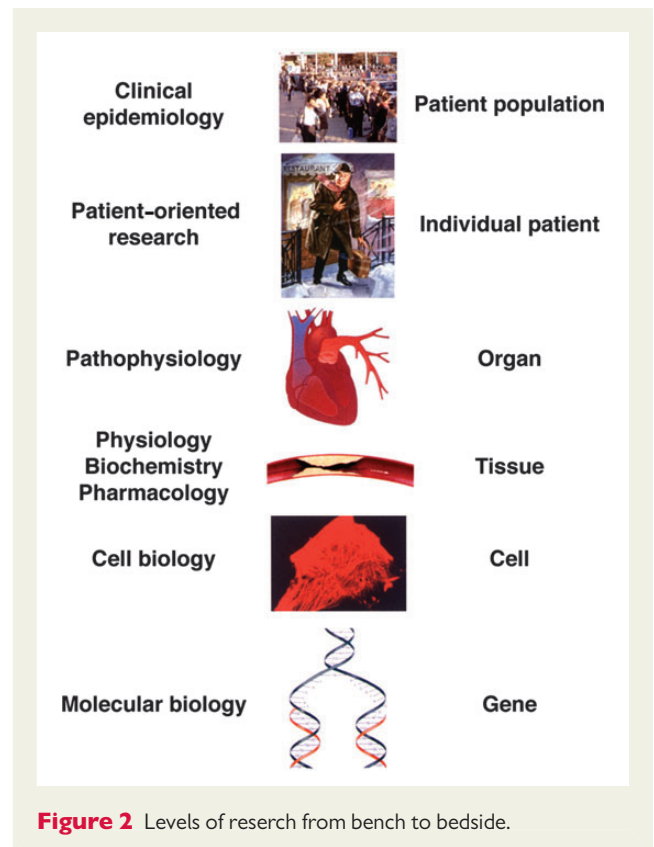
relationship.¹¹ Ever since then, the difference between association and causality has been stressed.¹²

In medicine, different levels of evidence have been distinguished (Figure 1), as follows: clinical intuition, unsystematic clinical experience, case reports and patient cohorts, pathophysiological concepts (the basis of most paradigms in medicine),⁸ small trials and meta-analyses or systematic reviews thereof, and finally, large randomized trials.

James Lind and scurvy

Scurvy is a disease which leads to open sores and loss of movement, a condition which, until the 19th century, was particularly prevalent among sailors and soldiers. The ship's surgeon of the British Royal Navy, James Lind, was the first to find a cure for the disease. While at sea in May 1747, Lind treated some of his sailors who were suffering from scurvy with oranges and lemons, while others received cider, vinegar, sulfuric acid or seawater, along with their usual food. Historically, this has to be considered the first randomized (although not blinded), controlled trial. In spite of the very small number of patients involved, the results conclusively showed that citrus fruits prevented the disease. Lind published his observation in 1753 in his '*Treatise on the Scurvy*'.¹³

Lind's approach was not adopted by medical researchers until the 20th century, when Austin Bradford Hill (1897–1991), an English epidemiologist and statistician, set out to test the effects of the recently discovered streptomycin in patients with tuberculosis. At this point, it had been recognized that biases of both the patient and the treating physician may influence the perception of the effectiveness of medical interventions. Tuberculosis was an endemic disease commonly treated by bed rest on the '*Magic Mountain*'¹⁴ and other institutions, mostly at high altitude. Hill wanted to prove the advantages of streptomycin compared with that standard treatment and developed the principle of randomization to exclude as many biases as possible. The results were a breakthrough, both for his scientific approach and for the treatment of tuberculosis. The trial lasted 6 months and involved 52 controls treated by bed rest and 55 patients receiving 2 g of streptomycin four times daily. As he wrote in his seminal article published in the *British Medical Journal* in 1948:¹⁵ '*The difference*

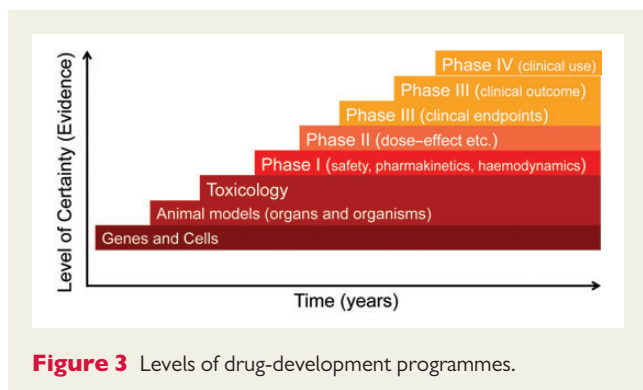


between the two series is statistically significant; the probability of it occurring by chance is less than one in a hundred.' Ever since then, randomization (today also with blinding of doctors and patients, if possible) and statistical analysis have become the cornerstones of clinical research.

From bench to bedside

It is obvious that any clinical trial rests on the results of often decades of basic research. Indeed, there are several levels of science involving genes, proteins, organelles and cells, tissues, organs, and finally, patients and populations (Figure 2). Evidence has to evolve over many steps in order to graduate from bench to bedside. This process is not unidirectional; indeed, a seminal observation may, for instance, start in a tissue, such as a blood vessel of an animal, where a novel phenomenon, e.g. endothelium-dependent relaxation, is observed,¹⁶ then may progress to organs and organisms,¹⁷ only to move down to the molecular level, where the responsible protein, i.e. endothelial nitric oxide synthase,¹⁸ is discovered. Clinical trials,^{19,20} Mendelian randomization studies and others, may follow later.

In drug discovery, the process is more unidirectional, starting with basic research in cells, tissues, and animals and then moving to phase I studies focusing on safety, pharmacokinetics, and haemodynamics. The dose–effect relationship is then investigated in phase II, while clinical endpoints are the focus of phase III studies (Figure 3). Dose is a difficult issue, particularly in the absence of reliable surrogate endpoints. Indeed, dosages used *in vitro* or in animal models are often several magnitudes higher than those effective and tolerated in humans.



Lost in translation

When moving through all these levels of research and development, concepts, drugs, and devices may be lost in translation. Why are things lost in translation? First, the hypothesis may be wrong, then the animal models used may not reflect human disease, the data may not be solid or may even be fraudulent,²¹ endpoints may not have been well chosen, unrecognized off-target effects may suddenly appear that outweigh the benefits, and finally, there are miscellaneous reasons.

Let us look at a few examples. In the 1980s and 1990s, restenosis after angioplasty or stenting was a real issue. At the same time, the vascular effects of angiotensin II were discovered, and researchers at Roche published an article in *Science*²² demonstrating that the angiotensin-converting enzyme (ACE) inhibitor cilazapril prevented intimal hyperplasia induced by vascular injury in the carotid artery of the rat. Swiftly, several clinical trials, MERCATOR²³ and MARCATOR,²⁴ were set up to prove these findings in patients undergoing angioplasty. As it turned out, cilazapril at either a high or a low dose did not prevent restenosis or improve outcomes. Obviously, the rat carotid artery was an inappropriate model, because most interventions worked that later proved ineffective at the clinical level. Once a new molecule, rapamycin, proved effective in the pig model of stent restenosis, the results could be confirmed at the clinical level.

Things can get worse; for example, TGN1412 (or CD28-SuperMAB) was the working name of a supposedly immunomodulatory drug originally intended for the treatment of B cell chronic lymphocytic leukaemia or rheumatoid arthritis.²⁵ In March 2006, six volunteers were entering a phase I trial at Northwick Park Hospital as the first humans to receive the drug. Unexpectedly, the drug caused catastrophic systemic organ failure due to a massive cytokine storm in the volunteers enrolled, despite it being administered at a dose 500 times lower than that found safe in animals. Obviously, the problems resulted from biological actions in humans not foreseen from the experiments in rats and mice.

Although mice share about 80% of their their working DNA with humans,²⁶ they are obviously at best a model; they are not humans. They may differ substantially in some respects, while they may be similar in others. Crossing the species border is always a risk in translational research.

Off-target effects are another problem. Often, novel therapeutic targets are identified in very distinct experimental settings. For instance, cyclo-oxygenase-2 inhibitors were developed to reduce

bleeding and increases in blood pressure associated with the use of non-steroidal anti-inflammatory drugs. Although these aims were partly achieved, rofecoxib was associated with an increased incidence of myocardial infarction, possibly due to prothrombotic effects,²⁷ while celecoxib is still being tested in the large PRECISION trial.²⁸ With an ever older population being treated in cardiovascular medicine, co-morbidities and drugs used to treat those, cardiovascular safety becomes an increasing issue that needs to be considered in any drug-development programme.

Another example is provided by drugs that raise high-density lipoprotein cholesterol (HDL-C) (Lüscher *et al.* in press). Epidemiologically, it appeared obvious that raising HDL-C would reduce cardiovascular events in patients at risk. The cholesterol ester transport protein inhibitors therefore raised big hopes;²⁹ and indeed, the first in its class, torcetrapib, more than doubled HDL-C levels, but unexpectedly increased mortality.³⁰ Later, basic research showed that torcetrapib increased aldosterone release from the adrenal glands and endothelin release from the vasculature, while suppressing endothelial nitric oxide synthase expression and endothelial function.³¹ These effects were considered off-target, because other molecules of the same class, such as dalcetrapib, did not share these properties. In phase II studies, such as *Dal-Vessel*, dalcetrapib increased HDL-C by 30% in patients with hyperlipidaemia and low HDL-C, while leaving blood pressure unchanged.³² However, dalcetrapib did not improve endothelial dysfunction or suppress markers of inflammation. In line with this, dalcetrapib was ineffective in patients after acute coronary syndromes in the large *Dal-Outcomes* trial.³³ Thus, it is likely that HDL-C dysfunction in patients with acute coronary syndromes may explain the neutral results, in spite of a marked rise in the lipoprotein.³⁴ Indeed, another HDL-C-raising drug, i.e. niacin, proved equally ineffective in two large outcome trials.^{35,36} Thus, HDL-C may be a marker rather than a therapeutic target, unless a drug also improves HDL-C dysfunction and protein composition³⁷ in patients with acute coronary syndromes or coronary artery disease, or the HDL-C paradigm is wrong altogether.

Therefore, surrogate endpoints are an important need (Table 1).^{38,39,40,41,42} While blood pressure⁴³ and low-density lipoprotein cholesterol are accepted surrogate endpoints predicting risk, and when lowered pharmacologically lead to a reduced risk, the record of other surrogates is less convincing.

For instance, in the 1970s, ventricular ectopic beats were considered ideal surrogates for patients at risk of sudden cardiac death, until the CAST trial⁴⁴ and the SWORD trial,⁴⁵ using antiarrhythmic drugs, such as encainide, flecainide, moricizine, or *d*-sotalol, respectively found an increased rather than decreased mortality, in spite of effective suppression of ventricular ectopic beats.

Likewise, in heart failure, exercise performance, haemodynamic improvements, and left ventricular ejection fraction have been used with disappointing results. Indeed, many drugs, such as inotropes or phosphodiesterase inhibitors, improved haemodynamics and exercise performance, but increased mortality.⁴⁶ Thus, the paradigm of stimulating the heart was falsified, while the concept of unloading it proved effective.⁴⁷ It appears that only a reduction of left ventricular remodelling and of brain natriuretic peptide⁴⁸ have some predictive value for clinical outcome in this patient population. Indeed, the lack of remodelling with endothelin antagonists⁴⁹ predicted negative outcome studies.⁵⁰

Table 1 Surrogate endpoints and their validity to predict major cardiovascular outcomes in different areas of cardiology

Disease	Surrogate endpoint (changes in)	Validity
Hypertension	Blood pressure ⁴³	++++
	Carotid intima-media thickness ⁴³	++
	Microalbuminuria ^a	++/?
	Flow-mediated dilatation ^{b,38}	++
	Left ventricular hypertrophy (ECG, echocardiography, magnetic resonance imaging) ⁴³	++
Lipids	Low-density lipoprotein cholesterol ⁴²	+++
	High-density lipoprotein cholesterol	—
	Carotid magnetic resonance imaging ^b	++
	Intravascular ultrasound ⁴⁰	++
	Coronary computed tomography ³⁹	?
	Optical coherence tomography ⁴¹	?
Diabetes	Glucose	++
	Haemoglobin 1 _{Ac}	++
	Microalbuminuria	++
Coronary artery disease	Quantitative coronary angiography	++
	Intravascular ultrasound ⁴⁰	++
	Coronary computed tomography ³⁹	?
	Optical coherence tomography ⁴¹	?
Acute coronary syndromes	Troponins	++
	Brain natriuretic peptide	++
	Infarct size (late enhancement in magnetic resonance imaging)	?
Heart failure	Exercise capacity ^{46,47}	—
	Haemodynamics (cardiac output etc.) ⁴⁷	—
	Ejection fraction	—
	Remodelling (left ventricular end-systolic volume) ⁴⁹	++
	Brain natriuretic peptide ^{47,48}	++
Sudden death	Premature ventricular beats ⁴⁴	—
	Late potentials	—
	Non-sustained ventricular tachycardia on Holter	—

The symbols '+' to '++++' indicate the degree of predictability of a change in each parameter for a change in major cardiovascular events; the symbol '?' indicates currently unknown.

^aAlthough considered predictive by many,⁴² in the ROADMAP trial, microalbuminuria changed favourably in spite of a neutral to negative effect on mortality (*N Engl J Med* 2011;**364**:907–917).

^bFlow-mediated dilatation was predictive in many situations except with estrogens and calcium antagonists, but it recently predicted the failure of darusentan.³¹ Its reproducibility depends on the experience of the core laboratory.³⁸

^cIn the Dal-Plaques study (*Lancet* 2011;**378**:1547–1559), carotid magnetic resonance imaging changed slightly, but favourably, in response to darusentan, while the large outcome trial was neutral.³³

^dCoronary computed tomography is highly predictive of future cardiovascular events, but its use in therapeutic trials has not yet been studied properly.³⁹

Why many research findings prove to be false

Thus, as predicted by Karl Popper,⁴ most research findings are eventually falsified at different levels of research. While some hypotheses and paradigms survive the entire process, others have to be dismissed at initial or later stages. The reasons are multiple, but may include the following:⁵¹ (i) inappropriate experimental models (i.e. cellular systems, animals); (ii) irreproducible findings (i.e. overstated, selected or fraudulent data, large number of tested relationships, 'hot' scientific field); (iii) study design (i.e. comparator groups, small sample size, wrong study population, extended flexibility in definitions of outcomes); (iv) small effect size; and (v) overwhelming intellectual or financial interests.^{52,53}

As outlined above, many findings in cellular systems and animal models cannot be reproduced at the clinical level, because they are limited to specific experimental conditions, due to species differences or inappropriate modelling of human disease. Currently, for convenience, costs, and legal as well as regulatory constraints, mainly rodents are used, although pigs and primates are closer to humans in many respects. Biological systems in animal models should be more carefully evaluated regarding their similarity to human biology. Possibly, humanized mice may be helpful.⁵⁴

Furthermore, not all research findings are reproducible, because they may require very specific experimental settings, are seen only in certain, but not other cell lines or animal strains, or have been overstated due to the enthusiasm of the investigators. Not uncommonly, parts of the results are not presented in the published manuscript in

order to pass the rigid peer review process, or certain experimental data are even suppressed.⁵⁵ Of note, an increasing number of manuscripts have had to be retracted after publication, particularly in high-impact journals.⁵⁶

In response to that unfortunate trend, C. Glenn Bayley recently published the six red flags to test scientific findings.⁵⁷ First, are experiments performed blinded? Second, were basic experiments appropriately repeated? Third, were all results presented? Fourth, were there positive and negative controls? Fifth, were reagents validated? And sixth, were statistical tests appropriate? It is obvious that bench experiments cannot be or are rarely performed in a blinded manner. Amazingly, suppression of data is common practice, as acknowledged by almost a third of the participating scientists in an anonymous survey.⁵⁵ Obviously, there may be good scientific reasons to do so, but then it should be clearly stated in the Methods section. That reagents have to be validated has recently been stressed by a study showing that dimethyl sulfoxide, a commonly used solvent, has profound biological effects.⁵⁸ Statistics of all seriously considered papers are currently checked by specialized editors in all high-impact journals, including the *European Heart Journal*.^{59,60} Finally, in 'hot' scientific fields there is a clear danger of publishing too quickly and too enthusiastically, as again stressed by fraud scandals affecting stem cell research.⁶¹

At the clinical level, the study design is particularly important. In general, non-randomized and smaller randomized studies are more commonly refuted by later research.⁵¹ For instance, an initial case-control study involving 1334 patients and controls suggested that an ACE polymorphism was associated with an increased incidence of myocardial infarction,⁶² a finding that became smaller and eventually absent in larger subsequent studies involving more than 10 000 individuals.⁶³ Registry data, even when analysed using modern statistics, such as propensity analysis,⁶⁴ are less reliable, although they reflect current practice. For instance, the nurses' health study suggested that hormone replacement therapy was protective in postmenopausal women,⁶⁵ a finding not confirmed in large randomized outcome trials.⁶⁶ Most probably, hormone use was a reflection of the health consciousness of the participants and not a causal factor.¹² Furthermore, post-marketing registries of novel compounds are prone to over-reporting, thereby providing a distorted estimate compared with established treatments.⁶⁷

Even randomized studies may be refuted over time, particularly the smaller ones. For instance, the QUIET trial,⁶⁸ involving 1750 patients with cardiovascular disease, found no benefit of ACE inhibition, while the HOPE trial,⁶⁹ enrolling 9297 patients, was positive. In clinical papers, appropriate power calculation is particularly crucial and increasingly difficult as event rates have dropped continuously in the last decades due to the increasing use of evidence-based therapies. Thus, larger and larger patient populations are required, particularly with non-inferiority designs.⁷⁰ Thus, for ethical and financial reasons, reliable surrogate endpoints with a high predictive value for major cardiovascular events would be crucial.

A major drawback of the results of clinical trials, when eventually translated into clinical practice, is the fact that only a minority of qualifying patients are enrolled and that those who are enrolled differ from non-participants. Study patients have different baseline characteristics with regard to age, co-morbidities, and drug treatments, among other factors, and accordingly, have a lower mortality and lower

event rate than non-participants.^{71–73} Finally, depending on inclusion and exclusion criteria, as well as the outcomes definitions used, the results of different trials may be difficult to compare. Thus, attempts have been made to harmonize major outcomes, as well as definitions of bleeding.^{74,75} Such attempts are crucial for comparison and for the further evaluation of trial results in all-comers registries.

Finally, it has been suggested that conflicts of interest affect results. Conflicts may be intellectual (mainly in basic and pathophysiological research), professional (mainly in device- and equipment-based research), and/or financial in nature. Particularly in clinical trials, the design may already be influenced by financial considerations (i.e. comparator, dose of comparator, patient population etc.).

The role of scientific journals

It is the aim of the peer review process common to all respected scientific journals to assess research findings critically with regard to their validity, importance, and novelty.^{76,77} Great care has to be taken in evaluating the design, methodology, and data analysis of a given manuscript in order to assure that the data are valid and eventually reproducible. Although less than perfect, the peer review process, particularly when involving three reviewers and knowledgeable editors, may pick up flaws and provide advice on how to improve the manuscript. Nevertheless, the process cannot completely avoid the possibility that some of the published papers are irreproducible or even have to be retracted.^{21,56} Increasingly, journal editorial offices receive allegations from other authors or whistleblowers on the validity or reproducibility of findings. To address this issue, the *ESC Journal Family* has initiated an independent Ethics Board, where such allegations will be handled.⁷⁸

There are conflicts of interest for editors also that may endanger a proper peer review and selection of manuscripts. In particular, papers reporting novel data of 'hot' areas may be accepted with lesser stringency. For instance, as with gene therapy research in the 1990s, stem cell research currently attracts a lot of attention; hence, even studies with minimal patient numbers are accepted.⁷⁹ Furthermore, pressures from industry, either open or under cover, may affect editorial decisions.⁸⁰ Thus, editors must be aware of these potential biases.

Thus, in summary, the road to evidence is long and winding indeed. As the evidence base of clinical medicine has grown, the process has become even longer and bumpier; as event rates have dropped and the most obvious facts have been discovered, it has become increasingly difficult to demonstrate incremental novelty and/or benefit beyond what has already been achieved. This may explain the increasing number of neutral trials in today's cardiovascular research. However, the lessons learned from the past may be helpful for discovery programmes of the future.

References

1. Matson W. *Grand Theories and Everyday Beliefs: Science, Philosophy, and Their Histories*. Oxford: Oxford University Press; 2011. p65–74.
2. Lüscher TF. Vom Symbol zum Organ. In: *Gedankenmedizin*. Heidelberg: Springer; 2010. p37–60.
3. Braunwald E. The rise of cardiovascular medicine. *Eur Heart J* 2012;**33**:838–845.
4. Popper K. *Conjectures and Refutations. The Growth of Scientific Knowledge*. London: Routledge and Kegan Paul; 1974.
5. Lüscher TF. Good publishing practice. *Eur Heart J* 2012;**33**:557–561.
6. Popper KR. *The logic of scientific discovery*. London: Taylor and Francis; 2002.

7. Taleb NN. *The Black Swan – the Impact of the Highly Improbable*. London: Penguin Books; 2008.
8. Kuhn TS. *The Structure of Scientific Revolution*. Chicago: University of Chicago Press; 2012.
9. Anitschkow N. Experimental arteriosclerosis in animals. In: Cowdry EV, ed. *Arteriosclerosis: a Survey of the Problem*. New York: Macmillan; 1933.
10. Dawber TR. *The Framingham Study. The Epidemiology of Atherosclerotic Disease. A Commonwealth Fund book*. Cambridge, MA: Harvard University Press; 1980.
11. 4S Investigators. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study. *Lancet* 1994;**344**: 1383–1389.
12. Lüscher TF. In search of the right word: a statement of the HEART Group on scientific language. *Eur Heart J* 2013;**34**:7–9.
13. Lind J. *Treatise on the Scurvy. In three parts*. 3rd ed., enlarged and improved. Printed for S. Crowder, D. Wilson, and G. Nicholls, T. Cadwell, T. Becket and Co., London; 1772.
14. Mann T. *The Magic Mountain*. London: Penguin; 1955.
15. Hill AB. Streptomycin treatment of pulmonary tuberculosis: a Medical Research Council investigation. *Br Med J* 1948;**769**–773.
16. Furchgott RF, Zawadzki JV. The obligatory role of endothelial cells in the relaxation of arterial smooth muscle by acetylcholine. *Nature* 1980;**288**:373–376.
17. Lüscher TF, Diederich D, Siebenmann R, Lehmann K, Stulz P, von Segesser L, Yang Z, Turina M, Grädel E, Weber E, Bühler FR. Difference between endothelium-dependent relaxations in arterial and in venous coronary bypass grafts. *N Engl J Med* 1988;**319**:462–467.
18. Förstermann U, Sessa WC. Nitric oxide synthases: regulation and function. *Eur Heart J* 2012;**33**:829–837.
19. Mancini JGB, Henry GC, Macaya C, O'Neill BJ, Pucillo AL, Carere RG, Wargovich TJ, Mudra H, Lüscher TF, Klibaner MI, Haber HE, Uprichard ACG, Pepine CJ, Pitt B. Angiotensin-converting enzyme inhibition with quinapril improves endothelial vasomotor dysfunction in patients with coronary artery disease: the TREND (Trial on reversing endothelial dysfunction) study. *Circulation* 1996;**94**:258–265.
20. Lüscher TF, Pieper M, Tendera M, Vrolix M, Rutsch W, van den Branden F, Gil R, Bischoff KO, Haude M, Fischer D, Meinertz T, Münzel T. A randomized placebo-controlled study on the effect of nifedipine on coronary endothelial function and plaque formation in patients with coronary artery disease: the ENCORE II study. *Eur Heart J* 2009;**30**:1556–1558.
21. Lüscher TF. The codex of science: honesty, precision, and truth—and its violations. *Eur Heart J* 2013;**34**:1018–1023.
22. Powell JS, Clozel JP, Müller RK, Kuhn H, Hefti F, Hosang M, Baumgartner HR. Inhibitors of angiotensin-converting enzyme prevent myointimal proliferation after vascular injury. *Science* 1989;**245**:186–188.
23. The MERCATOR study group. Does the new angiotensin converting enzyme inhibitor cilazapril prevent restenosis after percutaneous transluminal coronary angioplasty? Results of the MERCATOR study: a multicenter, randomized, double-blind placebo-controlled trial. *Circulation* 1992;**86**:100–110.
24. Berger PB, Holmes DR Jr, Ohman EM, O'Hanesian MA, Murphy JG, Schwartz RS, Serruys PW, Faxon DP. Restenosis, reocclusion and adverse cardiovascular events after successful balloon angioplasty of occluded versus nonoccluded coronary arteries. Results from the Multicenter American Research Trial With Cilazapril After Angioplasty to Prevent Transluminal Coronary Obstruction and Restenosis (MARCATOR). *J Am Coll Cardiol* 1996;**27**:1–7.
25. Hünig T. The storm has cleared: lessons from the CD28 superagonist TGN1412 trial. *Nat Rev Immunol* 2012;**12**:317–318.
26. Church DM, Goodstadt L, Hillier LW, Zody MC, Goldstein S, She X, Bult CJ, Agarwala R, Cherry JL, DiCuccio M, Hlavina W, Kapustin Y, Meric P, Maglott D, Birtle Z, Marques AC, Graves T, Zhou S, Teague B, Potamouis K, Churas C, Place M, Herschleb J, Runnheim R, Forrest D, Amos-Landgraf J, Schwartz DC, Cheng Z, Lindblad-Toh K, Eichler EE, Ponting CP, the Mouse Genome Sequencing Consortium. Lineage-specific biology revealed by a finished genome assembly of the mouse. *PLoS Biol* 2009;**7**:e1000112.
27. Mukherjee D, Nissen SE, Topol EJ. Risk of cardiovascular events associated with selective COX-2 inhibitors. *JAMA* 2001;**286**:954–959.
28. Becker MC, Wang TH, Wisniewski L, Wolksi K, Libby P, Lüscher TF, Borer JS, Mascette AM, Husni ME, Solomon DH, Graham DY, Yeomans ND, Krum H, Ruschitzka FT, Lincoff AM, Nissen SE, PRECISION Investigators. Rationale, design, and governance of Prospective Randomized Evaluation of Celecoxib Integrated Safety versus Ibuprofen Or Naproxen (PRECISION), a cardiovascular end point trial of nonsteroidal antiinflammatory agents in patients with arthritis. *Am Heart J* 2009;**157**:606–612.
29. Landmesser U, von Eckardstein A, Kastelein J, Deanfield J, Lüscher TF. Increasing high-density lipoprotein cholesterol by cholesteryl ester transfer protein-inhibition: a rocky road and lessons learned? The early demise of the dal-HEART programme. *Eur Heart J* 2012;**33**:1712–1715.
30. Barter PJ, Caulfield M, Eriksson M, Grundy SM, Kastelein JJ, Komajda M, Lopez-Sendon J, Mosca L, Tardif JC, Waters DD, Shear CL, Revkin JH, Buhr KA, Fisher MR, Tall AR, Brewer B. Effects of torcetrapib in patients at high risk for coronary events. *N Engl J Med* 2007;**357**:2109–2122.
31. Simic B, Herrmann M, Shaw SG, Bigler L, Stalder U, Dorries C, Besler C, Lüscher TF, Ruschitzka F. Torcetrapib impairs endothelial function in hypertension. *Eur Heart J* 2012;**33**:1615–1624.
32. Lüscher TF, Taddei S, Kaski JC, Jukema JW, Kallend D, Münzel T, Kastelein JJ, Deanfield JE. Vascular effects and safety of dalcetrapib in patients with or at risk of coronary heart disease: the dal-VESSEL randomized clinical trial. *Eur Heart J* 2012;**33**:857–865.
33. Schwartz GG, Olsson AG, Abt M, Ballantyne CM, Barter PJ, Brumm J, Chaitman BR, Holme IM, Kallend D, Leiter LA, Leitersdorf E, McMurray JJ, Mundt H, Nicholls SJ, Shah PK, Tardif JC, Wright RS, dal-OUTCOMES Investigators. Effects of dalcetrapib in patients with a recent acute coronary syndrome. *N Engl J Med* 2012;**367**: 2089–2099.
34. Besler C, Heinrich H, Rohrer L, Doerries C, Riwanto M, Shih DM, Chroni A, Yonekawa K, Stein S, Schaefer N, Mueller M, Akhmedov A, Daniil G, Manes C, Templin C, Wyss C, Maier W, Tanner FC, Matter CM, Corti R, Furlong C, Lusis AJ, Eckardstein AV, Fogelman AM, Lüscher TF, Landmesser U. Mechanisms underlying adverse effects of HDL on ENOS-activating pathways in patients with coronary artery disease. *J Clin Invest* 2011;**121**:2693–2708.
35. AIM-HIGH Investigators, Boden WE, Probstfield JL, Anderson T, Chaitman BR, Desvignes-Nickens P, Koprowicz K, McBride R, Teo K, Weintraub W. Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy. *N Engl J Med* 2011;**365**:2255–2267.
36. HPS 2-THRIVE Collaborative Group. HPS2-THRIVE randomized placebo-controlled trial in 25,673 high-risk patients of ER niacin/laropiprant: trial design, pre-specified muscle and liver outcomes, and reasons for stopping study treatment. *Eur Heart J* 2013;**34**:1279–1291.
37. Riwanto M, Rohrer L, Roschitzki B, Besler C, Mocharla P, Mueller M, Perisa D, Heinrich K, Altwegg L, von Eckardstein A, Lüscher TF, Landmesser U. Altered activation of endothelial anti- and proapoptotic pathways by high-density lipoprotein from patients with coronary artery disease: role of high-density lipoprotein-proteome remodeling. *Circulation* 2013;**127**:891–904.
38. Charakida M, Masi S, Lüscher TF, Kastelein JJP, Deanfield JE. Assessment of atherosclerosis: the role of flow-mediated dilatation. *Eur Heart J* 2010;**31**:2854–2861.
39. Achenbach S, Raggi P. Imaging of coronary atherosclerosis by computed tomography. *Eur Heart J* 2010;**31**:1442–1448.
40. Garcia-Garcia HM, Costa MA, Serruys PW. Imaging of coronary atherosclerosis: intravascular ultrasound. *Eur Heart J* 2010;**31**:2456–2469.
41. Prati F, Regar E, Mintz GS, Arbustini E, Di Mario C, Jang IK, Akasaka T, Costa M, Guagliumi G, Grube E, Ozaki Y, Pinto F, Serruys PWJ. Expert review document on methodology, terminology, and clinical applications of optical coherence tomography: physical principles, methodology of image acquisition, and clinical application for assessment of coronary arteries and atherosclerosis. *Eur Heart J* 2010;**31**: 401–415.
42. Reiner Z, Catapano AL, De Backer G, Graham I, Taskinen MR, Wiklund O, Agewall S, Alegria E, Chapman MJ, Durrington P, Erdine S, Halcox J, Hobbs R, Kjekshus J, Perrone Filardi P, Riccardi G, Storey RF, Wood D, The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). ESC/EAS Guidelines for the management of dyslipidaemias. *Eur Heart J* 2011;**32**:1769–1818.
43. Mancia G, Fagard R, Narkiewicz K, Redon J, Zanchetti A, Boehm M, Christiaens T, Cifkova R, De Backer G, Dominiczak A, Galderisi M, Grobbee DE, Jaarsma T, Kirchhof P, Kjeldsen SE, Laurent S, Manolis AJ, Nilsson PM, Ruilope LM, Schmieder RM, Sirnes PA, Sleight P, Viigimaa M, Waeber B, Zannad F, The Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology. 2013 ESH/ESC Guidelines for the management of arterial hypertension. *Eur Heart J* 2013;**34**: 2159–2219.
44. Echt DS, Liebson PR, Mitchell LB, Peters RW, Obias-Manno D, Barker AH, Arensburg D, Baker A, Friedman L, Greene HL, Huther ML, Richardson DW and the CAST Investigators. Mortality and morbidity in patients receiving encaidine, flecainide, or placebo. The Cardiac Arrhythmia Suppression Trial. *N Engl J Med* 1991;**324**:781–788.
45. Waldo AL, Camm AJ, deRuiter H, Friedman PL, MacNeil DJ, Pauls JF, Pitt B, Pratt CM, Schwartz PJ, Veltri EP. Effect of d-sotalol on mortality in patients with left ventricular dysfunction after recent remote myocardial infarction. The SWORD Investigators. *Survival With Oral d-Sotalol*. *Lancet* 1996;**348**:7–12.
46. Packer M, Carver JR, Rodeheffer RJ, Ivanhoe RJ, DiBianco R, Zeldis SM, Hendrix GH, Bommer WJ, Elkayam U, Kukin ML, Mallis GI, Sollano JA, Shannon J, Tandon PK, DeMets DL, and the PROMISE Study Research Group. Effect of oral milrinone on mortality in severe chronic heart failure. The PROMISE Study Research Group. *N Engl J Med* 1991;**325**:1468–1475.

47. McMurray JJV, Adamopoulos S, Anker SD, Auricchio A, Boehm M, Dickstein K, Falk V, Filippatos G, Fonseca C, Gomez-Sanchez MA, Jaarsma T, Køber L, Lip GYH, Maggioni AP, Parkhomenko A, Pieske BM, Popescu BA, Rønnevik PK, Rutten FH, Schwitler J, Seferovic P, Stepinska J, Trindade PT, Voors AA, Zeiher AM, The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012. *Eur Heart J* 2012;**33**:1787–1847.
48. Gardner RS, Özalp F, Munday AJ, Robb SD, McDonagh TA. N-terminal pro-brain natriuretic peptide. A new gold standard in predicting mortality in patients with advanced heart failure. *Eur Heart J* 2003;**24**:1735–1743.
49. Anand I, McMurray J, Cohn JN, Konstam MA, Nottter T, Quitzau K, Ruschitzka F, Lüscher TF, EARTH investigators. Long-term effects of darusentan on left-ventricular remodelling and clinical outcomes in the Endothelin A Receptor Antagonist Trial in Heart Failure (EARTH): randomised, double-blind, placebo-controlled trial. *Lancet* 2004;**364**:347–354.
50. Packer M, on behalf of the ENABLE investigators. Effects of the endothelin receptor antagonist bosentan on the morbidity and mortality in patients with chronic heart failure. Results of the ENABLE 1 and 2 Trial Program. Presented at the American College of Cardiology 2002.
51. Ioannidis JPA. Contradicted and initially stronger effects in highly cited clinical research. *JAMA* 2005;**294**:218–228.
52. Krinsky S. *Science in the Private Interest*. Lanham, MD: Bowman & Littlefield Publishers, Inc.; 2003. p28–33.
53. Lüscher TF, Gedankenmedizin F. In: *Conflict of Interest oder Interesse am Konflikt?* Heidelberg: Springer; 2010. p123–136.
54. Peltz G. Can 'humanized' mice improve drug development in the 21st century? *Trends Pharmacol Sci* 2013;**34**:255–260.
55. Fanelli D. How many scientists fabricate and falsify research? A systematic review and meta-analysis of survey data. *PLoS One* 2009;**4**:e5738.
56. Nallamothu BK, Lüscher TF. From impact to influence: measurement and the changing role of medical journals. *Eur Heart J* 2012;**33**:2892–2896.
57. Bagley CG. Six red flags for suspect work. *Nature* 2013;**497**:433–434.
58. Camici GG, Steffel J, Akhmedov A, Schaefer A, Baldinger J, Schulz U, Shojaaati K, Matter CM, Yang Z, Lüscher TF, Tanner FC. Dimethyl sulfoxide inhibits tissue factor expression, thrombus formation and vascular smooth muscle activation: a potential treatment strategy for drug-eluting stents. *Circulation* 2006;**114**:1512–1521.
59. Lüscher TF, Gersh B, Brugada J, Landmesser U, Ruschitzka F, Serruys PW. The *European Heart Journal* goes global: the road ahead of the editorial team 2009–2011. *Eur Heart J* 2009;**30**:1–5.
60. Lüscher TF, Brugada J, Gersh BJ, Landmesser U, Serruys PW, Murphy S, Dedecke S, Rogers S, Ruschitzka F. Happy birthday *European Heart Journal*: in 30 years, from Cinderella to centre stage. *Eur Heart J* 2010;**31**:1945–1950.
61. Francis DP, Mielewicz M, Zargar D, Cole GD. Autologous bone marrow-derived stem cell therapy in heart disease: discrepancies and contradictions. *Int J Cardiol*; doi: 10.1016/j.ijcard.2013.04.152. Published online ahead of print 26 June 2013.
62. Cambien F, Poirier O, Lecerf L, Evans A, Cambou JP, Arveiler D, Luc G, Bard JM, Bara L, Ricard S, Tiret L, Amouyel P, Albenc-Gelos F, Soubrier F. Deletion polymorphism in the gene for angiotensin-converting enzyme is a potent risk factor for myocardial infarction. *Nature* 1992;**359**:641–644.
63. Keavney B, McKenzie C, Parish S, Palmer A, Clark S, Youngman L, Delépine M, Lathrop M, Peto R, Collins R, for the International Studies of Infarct Survival (ISIS) Collaborators. Large-scale test of hypothesised associations between the angiotensin-converting-enzyme insertion/deletion polymorphism and myocardial infarction in about 5000 cases and 6000 controls. *Lancet* 2000;**355**:434–442.
64. Heinze G, Jüni P. An overview of the objectives of and the approaches to propensity analysis. *Eur Heart J* 2011;**32**:1704–1708.
65. Stampfer MJ, Colditz GA, Willett WC, Manson JE, Rosner B, Speizer FE, Hennekens CH. Postmenopausal estrogen therapy and cardiovascular disease. Ten-year follow-up from the nurses' health study. *N Engl J Med* 1991;**325**:756–762.
66. Hulley S, Grady D, Bush T, Furberg C, Herrington D, Riggs B, Vittinghoff E. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. Heart and Estrogen/progestin Replacement Study (HERS) Research Group. *JAMA* 1998;**280**:605–613.
67. Southworth MR, Rechman ME, Unger EF. Dabigatran and postmarketing reports of bleeding. *N Engl J Med* 2013;**368**:1272–1274.
68. Pitt B, O'Neill B, Feldman R, Ferrari R, Schwartz L, Mudra H, Bass T, Pepine C, Texter M, Haber H, Uprichard A, Cashin-Hemphill L, Lees RS, QUIET Study Group. The QUinapril Ischemic Event Trial (QUIET): evaluation of chronic ACE inhibitor therapy in patients with ischemic heart disease and preserved left ventricular function. *Am J Cardiol* 2001;**87**:1058–1063.
69. Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G. Effects of an angiotensin-converting-enzyme inhibitor ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. *New Engl J Med* 2000;**342**:145–153.
70. Head SJ, Kaul S, Bogers AJJC, Kappetein AP. Non-inferiority study design: lessons to be learned from cardiovascular trials. *Eur Heart J* 2012;**33**:1318–1324.
71. de Boer SPM, Lenzen MJ, Oemrawsingh RM, Simsek C, Duckers HJ, van der Giessen WJ, Serruys PW, Boersma E. Evaluating the 'all-comers' design: a comparison of participants in two 'all-comers' PCI trials with non-participants. *Eur Heart J* 2011;**32**:1854–1864.
72. Hordijk-Trion M, Lenzen MJ, Wijns W, de Jaegere PJ, Simoons ML, Scholte OP, Reimer WJM, Bertrand ME, Mercado N, Boersma E. Patients enrolled in coronary intervention trials are not representative of patients in clinical practice: results from the Euro Heart Survey on Coronary Revascularization. *Eur Heart J* 2006;**27**:671–678.
73. Vist GE, Bryant D, Somerville L, Birmingham T, Oxman AD. Outcomes of patients who participate in randomized controlled trials compared to similar patients receiving similar interventions who do not participate. *Cochrane Database Syst Rev* 2008; MR000009.
74. Steg PG, Huber K, Andreotti F, Arnesen H, Atar D, Badimon L, Bassand JP, De Caterina R, Eikelboom JA, Gulba D, Hamon M, Helft G, Fox KAA, Kristensen SD, Rao SV, Verheugt FWA, Widimsky P, Zeymer U, Collet JP. Bleeding in acute coronary syndromes and percutaneous coronary interventions: position paper by the Working Group on Thrombosis of the European Society of Cardiology. *Eur Heart J* 2011;**32**:1854–1864.
75. Kappetein AP, Head SJ, Genereux P, Piazza N, van Mieghem NM, Blackstone EH, Brott TG, Cohen DJ, Cutlip DE, van Es GA, Hahn RT, Kirtane AJ, Krucoff MW, Kodali S, Mack MJ, Mehran R, Rodés-Cabau J, Vranckx P, Webb JG, Windecker S, Serruys PW, Leon MB. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document. *Eur Heart J* 2012;**33**:2403–2418.
76. Lüscher TF, Gersh B, Hindricks G, Landmesser U, Nallamothu B, Ruschitzka F, Wijns W. The *European Heart Journal* on the move: can scientific publishing be further improved? *Eur Heart J* 2013;**34**:409–415.
77. Lüscher TF, Gersh B, Hindricks G, Landmesser U, Ruschitzka F, Wijns W. The best of the *European Heart Journal*: look back with pride. *Eur Heart J* 2012;**33**:1161–1171.
78. Lüscher TF, Simoons ML. The *European Heart Journal* launches Ethics Review Board (CardioPulse). *Eur Heart J* 2013;**34**:2107–2113.
79. Bolli R, Chugh AR, D'Amario D, Loughran JH, Stoddard MF, Ikram S, Beach GM, Wagner SG, Leri A, Hosoda T, Sanada F, Elmore JB, Goichberg P, Cappetta D, Solankhi NK, Fahsah I, Rokosh DG, Slaughter MS, Kajstura J, Anversa P. Cardiac stem cells in patients with ischaemic cardiomyopathy (SCIPIO): initial results of a randomised phase 1 trial. *Lancet* 2011;**378**:1847–1857.
80. Lüscher TF, Landmesser U, Ruschitzka F. Standing firm—the *European Heart Journal*, scientific discoveries and the industry. *Eur Heart J* 2010;**31**:1157–1158.