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Rethinking the appraisal and approval of drugs for type 2 diabetes mellitus

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The process for approving new drugs for type 2 diabetes illustrates the significant shortcomings of the regulatory standards for licensing, reimbursing, and adopting new drugs. Regulatory reform is needed to improve the real-world therapeutic value of anti-diabetic drugs.

Background

The overarching aim of drug regulation is to ensure that only effective and safe treatments reach patients. Ideally, regulatory decisions are based on good quality data from large trials measuring real-world, patient-centred outcomes. Licensing agencies, however, routinely permit the market entry of treatments on the basis of small placebo-controlled trials evaluating short-term, surrogate endpoints in selected populations. Consequently, medicines are commonly prescribed in the absence of good quality data on their long-term benefits and harms.[1,2] Current licensing standards are inadequate to predict the real-world therapeutic value of new medications.[3]

This is particularly problematic for preventive treatments given to large populations, which should be subject to a high standard of proof of benefit, and absence of significant harm. These drugs present interesting challenges, firstly because the real-world benefits often take many years to arise, and secondly because those benefits are often modest, although clinically significant. Trials should quantify the benefits and harms for the various populations that will use these drugs, ideally using pre-specified subgroups of sufficient size. This would provide clinicians and patients with dependable knowledge for shared decision-making.

In this paper, we focus on the regulatory appraisal and approval of new drugs for type 2 diabetes mellitus. Diabetes is a common condition that requires long-term pharmacotherapy. The global prevalence of diabetes was an estimated 347 million people in 2008, and it is expected to rise exponentially over the next decades.[4] With more than 30 anti-diabetic agents available on the market, the process for licensing new drugs for diabetes highlights the salient shortcomings of the evidence standards for licensing, reimbursing, and adopting new preventive drugs. Blood glucose lowering is the only benchmark used by regulatory agencies to grant market approval to anti-diabetic drugs (**Box 1**). For most anti-diabetic drugs in current use, there is insufficient evidence from randomised trials about their long-term clinical benefits or harms. We propose and discuss two alternative regulatory models for remedying this situation.

Time to curb regulatory enthusiasm for "timely market access"

The low bar for market entry set by licensing agencies, coupled with a quickly expanding diabetes economy created by guidelines, targets, and the rapidly rising prevalence of diabetes in emerging markets, encourages pharmaceutical firms to develop ever-increasing numbers of glucose-lowering therapies. There are currently over 200 molecules in the development pipeline.[5,6] In recent years, "timely market access" has become a regulatory orthodoxy that has led to a substantial reduction in the review times for drug applications.[7] This facilitates widespread use of treatments without adequate data on their risk-benefit ratio, and reduces the market incentive for high quality evidence. Over the past two decades, there has been an increase in drug withdrawals and black-box warnings.[8,9] The glucose-lowering drug rosiglitazone highlights the need for regulatory reform.[10] Initially heralded as a breakthrough drug, rosiglitazone was later found to increase the risk of cardiovascular adverse events and was withdrawn from European markets in 2010.[11,12]

We outline two alternative regulatory strategies that could improve the real-world therapeutic value of anti-diabetic drugs. Both strategies require long-term data on patient-centred outcomes in a timely manner to allow clinicians and patients to make informed decisions. Each strategy has important advantages and disadvantages (**Table**), and each carries significant administrative and financial costs. These costs should be weighed against the health benefits of a future scenario in which the only anti-diabetic agents used in clinical practice are those that have demonstrable effects on clinical outcomes – the sole purpose of preventive treatment. Our proposals are relevant to other preventive medications taken by large numbers of asymptomatic individuals for long periods of time. These strategies should be considered alongside other approaches aimed at generating and disseminating evidence for more informed patients and clinicians (**Box 2**).

Raising the bar for market entry by licensing agencies

The first potential strategy is to raise the evidence standards for approving new drugs by licensing agencies.[13-16] Licensing agencies in the US (FDA) and Europe (EMA) usually require only small trials enrolling 2,000-3,000 patients, and few of these patients are studied for longer than six months. These trials also rarely include key target groups for prescription in everyday clinical practice, namely the elderly patients with multimorbidities who are most likely to receive anti-diabetic medications.[17] By excluding such populations, the current regulatory environment results in *de facto* testing of new drugs in actual clinical practice. Also, pivotal trials rarely provide the necessary information about the relative benefits and harms of new versus older agents.[13,18]

Raising the bar at point of market entry would require firms to conduct large, active-comparator trials of new agents versus existing ones, measuring outcomes in real-world populations. Under this strategy, regulators would require trials lasting longer than current phase 3 trials, most of which measure only surrogate endpoints. Such trials would need to be simple pragmatic trials, recruiting patients who are likely to use the drug in clinical settings, and allowing providers to optimise treatment according to patients' needs – and not according to strict protocols.[19] This would provide realistic and timely estimates of the comparative effectiveness of new anti-diabetic agents.

It is often important to have several drug options available on the market to allow clinicians and patients to make shared decisions based on individual characteristics, responses, side effects, and preferences. Requiring comparative evidence at the time of market approval need not mean that only drugs demonstrating superiority over existing alternatives are approved.[18] Timely comparisons of new and existing agents may, however, deter the market entry of dramatically inferior or harmful drugs.

Future trials would need to evaluate outcomes that matter to patients and their caregivers – collectively known as "patient-centred outcomes." According to Guyatt and colleagues, a

patient-centred outcome must meet the following test: "Were it to be the only thing that changed, patients would be willing to undergo a treatment with associated risk, cost, or inconvenience."[20] Among such outcomes, reduction in death is of the highest significance; others include myocardial infarction, stroke, loss of vision, renal failure, amputation, neuropathy, and erectile dysfunction. Other key outcomes that influence patient independence, function, and quality of life are drug-related harms. Clinical trial publications generally fail to report adequate data on the timing, severity, and frequency of such harms, hindering a meaningful evaluation of long-term safety. Such outcomes should be routinely reported in a standardized fashion in future publications.

Since 2008, the FDA has asked pharmaceutical companies to demonstrate the cardiovascular neutrality of new anti-diabetic medications before they can be granted full market approval. The FDA considers new anti-diabetic drugs to have cardiovascular neutrality if the upper boundary of the 95% confidence interval for the hazard ratio is <1.3; if it is between 1.3 and 1.8, approval is conditional on post-marketing evidence. This is a major step in the right direction. But by falling short of requiring evidence of cardiovascular benefit, the FDA may indirectly discourage companies from investing in large trials to demonstrate such benefit.[21] The regulatory agencies also rarely follow up on companies that have agreed to do post-licensing, cardiovascular safety studies.[22] Requiring evidence of cardiovascular safety prior to approval would ensure that new drugs with no proven safety record are not widely used upon market entry. Research has shown that it is difficult to shift established prescribing patterns, even when new data from well-publicised studies become available.[23]

Pharmaceutical companies often contend that having to demonstrate cardiovascular benefit would set an unreasonably high hurdle for the development of new therapies. However, there is no evidence that raising the bar for market entry of new medications by licensing agencies deters innovation in the sector or hinders anti-diabetic drug development.[16,21] Nevertheless, licensing agencies are considering moving towards an adaptive licensing model, whereby approval is based on iterative phases of evidence generation and regulatory assessment[24] although the details of such adaptive mechanisms are unclear. The premise of adaptive licensing is to tolerate greater uncertainty at the time of approval to allow for early patient access to new drugs while further delaying the generation of long-term evidence until after market entry. While this process may be valid for severe, fast progressing, and life-threatening conditions for which no successful or safe treatment exists (e.g., rapidly fatal malignancies), given the number of agents already available, many of which have themselves not yet been adequately assessed for their impact on patient-centred outcomes, there is no pressing need for accelerated access to new glucose-lowering drugs for type 2 diabetes. There is therefore no reason why the FDA and EMA should tolerate a high degree of uncertainty about the long-term benefits and harms of such drugs.

Raising the bar for market entry by health technology assessment agencies

Licensing agencies are not alone in permitting anti-diabetic medications to enter the market on the basis of weak evidence. Many European countries have national health technology assessment (HTA) bodies, which provide evidence to support payer and prescriber decisions on the adoption, reimbursement, and use of new drugs. These organisations are expected to block market entry for products that do not provide genuine long-term benefits.[25] Therefore a second potential strategy to improve the regulation of anti-diabetic medications is to raise the standards of evidence required for approval by HTA agencies.

The current regulatory environment poses significant challenges for HTA bodies, such as the UK National Institute for Health and Care Excellence (NICE). Although NICE ostensibly has higher standards of evidence (e.g., real-world clinical data) than licensing agencies, it has limited resources and powers to enforce the conduct of new clinical studies.[26] In the absence of meaningful long-term data, NICE often depends on mathematical models of clinical and cost-effectiveness to approve or reject the market entry of new medicines. Such models

generally extrapolate from the short-term trial findings previously submitted to licensing agencies, and medicines are often approved based on impacts on surrogate markers such as glycaemia and body weight, despite significant remaining uncertainty about the long-term effects.

The second regulatory strategy would maintain the existing evidence standards within licensing agencies, but would ensure that new drugs for type 2 diabetes are approved by HTA agencies only when there is evidence of clear benefit on endpoints that are important to patients. This strategy would require manufacturers to gather evidence on real-world effectiveness, and it would minimise the number of patients exposed unnecessarily to uncertainty or harm.

A key component of this strategy would be determining the fate of new drugs while evidence on real-world effectiveness and safety is emerging. HTA agencies may need to sign "managed entry agreements" with pharmaceutical companies to hedge against uncertainties at the time of market approval regarding long-term clinical effects.[27,28] These schemes grant companies market access in return for achieving outcome targets (e.g., cardiovascular benefits). Over the past few years, such schemes have become more common in Europe and the US.[29,30]

Managed entry agreements can take many forms and can be incorporated into novel regulatory pathways, including adaptive licensing. For example, a new anti-diabetic medication could be "Approved for Randomisation" whereby the HTA agency asks a pharmaceutical company to gather more evidence about the long-term cardiovascular benefits and harms of its product – relative to other drugs in the same therapeutic class – in low-cost, head-to-head randomised trials.[31] It is increasingly feasible to embed such simple trials in clinical practice, with follow-up data on real-world outcomes such as myocardial infarction, or death, extracted from routinely collected administrative data and electronic health records.[32] Any clinician or patient seeking to access a new diabetes medication which currently lacks adequate evidence of benefit could be requested to specify the treatment option they would have used before the drug was approved. The patient would then be randomly assigned to receive the new drug or the active, standard-of-care comparator.

Depending on the configuration of the health service or insurance scheme, the agency may choose to fully or partly reimburse the medicine during the period of evidence collection, and subsequently re-assess its decision. If a treatment does demonstrate the benefits predicted by the company, then the drug can simply be upgraded to full HTA approval. If a treatment fails to meet the pre-specified targets (e.g., equivalent benefits and harms with existing agents on long-term outcomes), the agency could then: decline to pay the withheld portion of procurement costs for the drug; invite the company to decrease the price to reflect the poorer outcomes; downgrade the drug to HTA-unapproved; or suggest withdrawal of the drug from the market.

Managed entry agreements, however, have limitations. At present, changing the coverage status of a previously-reimbursed drug – or withdrawing an already approved product – can pose significant political challenges for HTA agencies.[30] Such agreements may also be operationally complex, costly, and difficult to implement. However, efforts are underway to improve the data infrastructure to collect valid information on relevant outcomes. Previous managed entry agreements have relied on observational designs to collect information on long-term outcomes. Post-approval data collection mechanisms considered for novel adaptive licensing models similarly rely on registries, cohorts, and other observational studies rather than reliable randomised trial data.[24,33] The limited experience from the US and UK suggests that, in the absence of randomisation, it is difficult to attribute observed differences in patient outcomes to the different drugs received.[34] Randomising patients into different drug groups would significantly improve the validity of studies on which managed

entry agreements are based.[35]

Conclusion

By accepting glucose-lowering as the primary yardstick by which to evaluate the effectiveness of new drugs for diabetes, regulators currently send the wrong signal to decision makers in health systems. It is wrong to imply to clinicians and patients that any drug that successfully lowers glucose levels will also achieve meaningful reductions in risk of patient-relevant micro- and macrovascular outcomes, unless this assertion has been reliably demonstrated for that specific agent in clinical trials.

There is a need to identify a feasible and cost-effective approach for both regulators and pharmaceutical companies that incentivises the production of new drugs and practical evidence. We suggest that one simple question should guide all decisions made by regulators, doctors, payers, patients, and policy-makers faced with new anti-diabetic drug applications: do we have clear evidence that this drug improves the outcomes that matter to patients?

Key Points

- Regulators permit glucose lowering drugs onto the market with suboptimal evidence which is inadequate to inform patients, clinicians, regulators, and payers.
- HTA bodies such as NICE then facilitate the use of such drugs, again without incentivising the production of good quality evidence.
- Better regulatory strategies are needed to generate long-term data on clinical outcomes in a timely manner.
- The first potential strategy is to raise the standards of evidence for approving new anti-diabetes drugs by licensing agencies.
- The second potential strategy is to raise the bar for covering and reimbursing new anti-diabetes drugs by health technology assessment agencies.

Contributors and Sources

HN and JSY devised the article. HN wrote the first draft. RH, OJW, BG, and JSY significantly contributed to subsequent drafts. All have read and agreed to the final version. HN is guarantor.

Conflicts of Interest

We declare no conflicts of interest. BG receives income outside of his medical / academic salary from speaking and writing for lay audiences of problems in science and medicine, including those raised here.

References

1. Avorn J. *Powerful medicines: The benefits, risks, and costs of prescription drugs.* Random House LLC; 2008.
2. Goldacre B, Smeeth L. Mass treatment with statins. *Bmj.* 2014;349:g4745.
3. Naci H, Ioannidis JP. How Good is" Evidence" from Clinical Studies of Drug Effects and Why Might Such Evidence Fail in the Prediction of Clinical Utility of Drugs? *Annual Review of Pharmacology and Toxicology.* 2014;55(1).

4. Whiting DR, Guariguata L, Weil C, Shaw J. IDF diabetes atlas: global estimates of the prevalence of diabetes for 2011 and 2030. *Diabetes research and clinical practice.* 2011;94(3):311-321.
5. PhRMA. Biopharmaceutical Research Companies Are Developing 180 Medicines to Treat Diabetes and Related Conditions. 2014; http://www.phrma.org/sites/default/files/pdf/diabetes2014.pdf. Accessed January 11, 2015.
6. International Federation of Pharmaceutical Manufacturers & Associations. The Pharmaceutical Industry and Global Health. 2012; http://www.ifpma.org/fileadmin/content/Publication/2013/IFPMA_-_Facts_And_Figures_2012_LowResSinglePage.pdf. Accessed January 11, 2015.
7. Philipson TJ, Berndt ER, Gottschalk AH, Strobeck MW. *Assessing the safety and efficacy of the FDA: the case of the Prescription Drug User Fee Acts.* National Bureau of Economic Research;2005.
8. Carpenter D, Zucker EJ, Avorn J. Drug-review deadlines and safety problems. *New England Journal of Medicine.* 2008;358(13):1354-1361.
9. Carpenter D, Chattopadhyay J, Moffitt S, Nall C. The complications of controlling agency time discretion: FDA review deadlines and postmarket drug safety. *American Journal of Political Science.* 2012;56(1):98-114.
10. Cohen D. Rosiglitazone: what went wrong? *Bmj.* 2010;341.
11. Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. *New England Journal of Medicine.* 2007;356(24):2457-2471.
12. Home PD, Pocock SJ, Beck-Nielsen H, et al. Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes (RECORD): a multicentre, randomised, open-label trial. *The Lancet.* 2009;373(9681):2125-2135.
13. Sorenson C, Naci H, Cylus J, Mossialos E. Evidence of comparative efficacy should have a formal role in European drug approvals. *British Medical Journal.* 2011;343(7822):d4849-d4849.
14. Alexander GC, O'Connor AB, Stafford RS. Enhancing prescription drug innovation and adoption. *Annals of internal medicine.* 2011;154(12):833-837.
15. O'Connor AB. Building comparative efficacy and tolerability into the FDA approval process. *Jama.* 2010;303(10):979-980.
16. Naci H, Cylus J, Vandoros S, Sato A, Perampaladas K. Raising the bar for market authorisation of new drugs. *Bmj.* 2012;345(7869):25-28.
17. Duijnhoven RG, Straus SM, Raine JM, de Boer A, Hoes AW, De Bruin ML. Number of patients studied prior to approval of new medicines: a database analysis. *PLoS medicine.* 2013;10(3):e1001407.
18. Stafford RS, Wagner TH, Lavori PW. New, but Not Improved? Incorporating Comparative-Effectiveness Information into FDA Labeling. *New England Journal of Medicine.* 2009;361(13):1230-1233.
19. Sonnad SS, Mullins CD, Whicher D, Goldsack JC, Mohr PE, Tunis SR. Recommendations for the design of Phase 3 pharmaceutical trials that are more informative for patients, clinicians, and payers. *Contemp Clin Trials.* 2013;36(2):356-361.
20. Guyatt GH, Haynes RB, Jaeschke RZ, et al. Users' Guides to the Medical Literature: XXV. Evidence-based medicine: principles for applying the Users' Guides to patient care. Evidence-Based Medicine Working Group. *Jama.* 2000;284(10):1290-1296.
21. Menon V, Lincoff AM. Cardiovascular safety evaluation in the development of new drugs for diabetes mellitus. *Circulation.* 2014;129(25):2705-2713.
22. Nissen SE. Setting the RECORD straight. *Jama.* 2010;303(12):1194-1195.
23. Jackevicius CA, Tu JV, Ross JS, Ko DT, Carreon D, Krumholz HM. Use of fibrates in the United States and Canada. *Jama.* 2011;305(12):1217-1224.

24. Eichler HG, Oye K, Baird LG, et al. Adaptive licensing: taking the next step in the evolution of drug approval. *Clin Pharmacol Ther.* 2012;91(3):426-437.
25. Chalkidou K, Tunis S, Lopert R, et al. Comparative Effectiveness Research and Evidence- Based Health Policy: Experience from Four Countries. *Milbank Quarterly.* 2009;87(2):339-367.
26. Chalkidou K, Hoy A, Littlejohns P. Making a decision to wait for more evidence: when the National Institute for Health and Clinical Excellence recommends a technology only in the context of research. *Journal of the Royal Society of Medicine.* 2007;100(10):453-460.
27. Adamski J, Godman B, Ofierska-Sujkowska G, et al. Risk sharing arrangements for pharmaceuticals: potential considerations and recommendations for European payers. *BMC health services research.* 2010;10:153.
28. Cook JP, Vernon JA, Manning R. Pharmaceutical risk-sharing agreements. *PharmacoEconomics.* 2008;26(7):551-556.
29. Ferrario A, Kanavos P. Dealing with uncertainty and high prices of new medicines: A comparative analysis of the use of managed entry agreements in Belgium, England, the Netherlands and Sweden. *Social science & medicine (1982).* 2015;124:39-47.
30. Neumann PJ, Chambers JD, Simon F, Meckley LM. Risk-sharing arrangements that link payment for drugs to health outcomes are proving hard to implement. *Health Affairs.* 2011;30(12):2329-2337.
31. Staa TP, Goldacre B, Gulliford M, et al. Pragmatic randomised trials using routine electronic health records: putting them to the test. *Bmj.* 2012;344:e55.
32. Lauer MS, D'Agostino RB, Sr. The randomized registry trial--the next disruptive technology in clinical research? *N Engl J Med.* 2013;369(17):1579-1581.
33. Soumerai SB, Starr D, Majumdar SR. How Do You Know Which Health Care Effectiveness Research You Can Trust? A Guide to Study Design for the Perplexed. *Prev Chronic Dis.* 2015;12:E101.
34. Raftery J. Multiple sclerosis risk sharing scheme: a costly failure. *Bmj.* 2010;340:c1672.
35. van Staa TP, Dyson L, McCann G, et al. The opportunities and challenges of pragmatic point-of-care randomised trials using routinely collected electronic records: evaluations of two exemplar trials. *Health Technol Assess.* 2014;18(43):1-146.
36. Cade WT. Diabetes-related microvascular and macrovascular diseases in the physical therapy setting. *Physical therapy.* 2008;88(11):1322-1335.
37. Yudkin JS, Richter B, Gale EA. Intensified glucose lowering in type 2 diabetes: time for a reappraisal. *Diabetologia.* 2010;53(10):2079-2085.
38. Boussageon R, Bejan-Angoulvant T, Saadatian-Elahi M, et al. Effect of intensive glucose lowering treatment on all cause mortality, cardiovascular death, and microvascular events in type 2 diabetes: meta-analysis of randomised controlled trials. *Bmj.* 2011;343.
39. Hemmingsen B, Lund SS, Gluud C, et al. Intensive glycaemic control for patients with type 2 diabetes: systematic review with meta-analysis and trial sequential analysis of randomised clinical trials. *Bmj.* 2011;343.
40. Boussageon R, Supper I, Bejan-Angoulvant T, et al. Reappraisal of Metformin Efficacy in the Treatment of Type 2 Diabetes: A Meta-Analysis of Randomised Controlled Trials. *PLoS Med.* 2012;9(4):e1001204.
41. Huang ES, Brown SES, Ewigman BG, Foley EC, Meltzer DO. Patient Perceptions of Quality of Life With Diabetes-Related Complications and Treatments. *Diabetes Care.* 2007;30(10):2478-2483.
42. Ray KK, Seshasai SRK, Wijesuriya S, et al. Effect of intensive control of glucose on cardiovascular outcomes and death in patients with diabetes mellitus: a meta-analysis of randomised controlled trials. *The Lancet.* 2009;373(9677):1765-1772.
43. Graham DJ, Ouellet-Hellstrom R, MaCurdy TE, et al. Risk of acute myocardial infarction, stroke, heart failure, and death in elderly Medicare patients treated with rosiglitazone or pioglitazone. *Jama.* 2010;304(4):411-418.

44. Nissen SE, Wolski K, Topol EJ. Effect of muraglitazar on death and major adverse cardiovascular events in patients with type 2 diabetes mellitus. *Jama.* 2005;294(20):2581-2586.
45. Vijan S, Sussman JB, Yudkin JS, Hayward RA. Effect of patients' risks and preferences on health gains with plasma glucose level lowering in type 2 diabetes mellitus. *JAMA Intern Med.* 2014;174(8):1227-1234.
46. Lipska KJ, Ross JS, Wang Y, et al. National Trends in US Hospital Admissions for Hyperglycemia and Hypoglycemia Among Medicare Beneficiaries, 1999 to 2011. *JAMA internal medicine.* 2014.
47. Hoffmann TC, Del Mar C. Patients' Expectations of the Benefits and Harms of Treatments, Screening, and Tests: A Systematic Review. *JAMA internal medicine.* 2014.
48. Price H, Thorne K, Dukat A, Kellett J. European physicians overestimate life expectancy and the likely impact of interventions in individuals with Type 2 diabetes. *Diabetic Medicine.* 2009;26(4):453-455.

Box 1. The link between glucose control and diabetic complications

It is important to examine the relationship between glucose control and diabetic complications.

Type 2 diabetes mellitus and its complications:

- Type 2 diabetes is defined by a particular threshold of blood glucose, and it is characterised by an increased risk of adverse health outcomes caused by vascular damage.
- Macrovascular complications of diabetes include coronary artery disease, peripheral arterial disease, and stroke; these are responsible for the vast majority of early deaths among people with diabetes.
- Microvascular complications include nephropathy, neuropathy, and retinopathy.[36]

Is there a strong link between blood glucose and diabetes complications?

- Complications of diabetes show a correlation with blood glucose levels, which is stronger for microvascular than for macrovascular complications.
- The correlation between blood glucose levels and complications has led to the widespread acceptance for blood glucose lowering as a valid surrogate measure of diabetes-related micro- and macrovascular adverse events.
- Existing evidence shows that levels of cholesterol and blood pressure are stronger risk factors for several macrovascular outcomes in diabetes than blood glucose levels.[37]

Are anti-diabetic medications effective in reducing the risk of complications?

- While effective in reducing the risk of microvascular complications, most of the drugs currently used to lower blood glucose levels have not been shown in randomised trials to reduce the rates of macrovascular complications.[38-40]
- In fact, treatment with anti-hypertensives or statins leads to larger reductions in cardiovascular risk than treatment with anti-diabetic medications.
- Intensified glucose lowering also has a greater negative impact on quality of life than lowering cholesterol or blood pressure.[41]
- Several anti-diabetic drugs have been found to increase the risk of cardiovascular complications.[11,38,42-44]
- The net benefits of available anti-diabetic medications are generally modest, and vary widely depending on individual characteristics and preferences.[45]
- There is growing evidence that the harms of tightly controlling blood glucose in the elderly often outweigh the benefits, with hypoglycaemia now overtaking hyperglycaemia as a cause for hospital admission in this group.[46]

Box 2. Beyond regulation: better dissemination and informed decision-makers

Physicians and patients often have exaggerated expectations of drug benefits[47,48] Undue regulatory emphasis on blood glucose-lowering may mislead patients into concluding that efforts aimed at reducing levels of this surrogate endpoint will successfully lower their risk of important macrovascular outcomes.

What can be done beyond regulation to remedy this situation?

- Clearer dissemination of evidence to both clinicians and patients may send a market signal, albeit less efficiently than HTA non-approval, by rewarding drugs with better evidence through higher prescription rates.
- There is a need for sustained improvement of mechanisms to disseminate knowledge and critical appraisal skills to clinicians, and ideally to those patients who are engaged with evidence.
- Future efforts aimed at improving evidence dissemination should be reinforced by a frank discussion with patients on the strengths and weaknesses of evidence for surrogate and clinical outcomes.
- In clinical practice guidelines, professional societies could prioritise clinicians communicating the benefits, risks, and harms of drugs to individuals, as well as the remaining uncertainties.
- Patient groups should be encouraged to prioritise their existing work on encouraging patients to ask for evidence.
- In line with best practice, clinicians should be encouraged to elicit and respect patients' individual preferences to facilitate shared decision-making.

Table – Advantages and disadvantages of two alternative regulatory strategies that could improve the real-world therapeutic value of anti-diabetic drugs

	Advantages	**Disadvantages**
<u>Strategy 1</u>: **Higher evidence standards for approving new anti-diabetic drugs by licensing agencies**	Only allow market entry of products that offer meaningful therapeutic benefit (i.e., equivalence to existing alternatives in terms of benefit and harm outcomes) Generate long-term evidence on comparative effectiveness in real-world populations in a timely manner before prescribing patterns are established	Potential delays in market entry of new anti-diabetic medications High hurdle for the development of new therapies
<u>Strategy 2</u>: **Higher evidence standards for covering and reimbursing new drugs by national health technology assessment (HTA) agencies**	Maintain the existing evidence standards within licensing agencies Ensure that new drugs are approved by HTA agencies only when there is evidence of clear benefit on important outcomes (i.e., equivalence to existing alternatives in terms of benefit and harm outcomes) Under managed entry agreements (e.g., “approved for randomization”), ensure patient access to new medications while new evidence is generated	Managed entry agreements are difficult to administer due to challenges in evidence generation in clinical practice, particularly for outcomes that are not routinely collected in electronic records Once new evidence is generated, changing the coverage status of a previously-reimbursed drug, or withdrawing an already-approved product, is politically challenging