

ANALYSIS



Rethinking the appraisal and approval of drugs for type 2 diabetes

Huseyin Naci and colleagues call for improvements in the regulatory standards for licensing, reimbursing, and adopting new preventive drugs to ensure that treatments for type 2 diabetes really benefit patients

Huseyin Naci *assistant professor of health policy*¹, Richard Lehman *senior research fellow*², Olivier J Wouters *researcher*¹, Ben Goldacre *senior clinical research fellow*³, John S Yudkin *emeritus professor of medicine*⁴

¹LSE Health, Department of Social Policy, London School of Economics and Political Science, London, UK; ²Nuffield Department of Primary Care Health Sciences, University of Oxford, Oxford, UK; ³Centre for Evidence Based Medicine, Nuffield Department of Primary Care Health Sciences, University of Oxford; ⁴Division of Medicine, University College London, London, UK

The 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 approve treatments on the basis of small placebo controlled trials evaluating short term, surrogate endpoints in selected populations. Consequently, medicines are commonly prescribed without 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 appreciable harm. These drugs present interesting challenges because, firstly, the real world benefits often take many years to arise and, secondly, those benefits are often modest, although clinically important. Trials should quantify the benefits and harms for the various populations that will use these drugs, ideally using prespecified subgroups of sufficient size. This would provide clinicians and patients with dependable knowledge for shared decision making. In this article we use the example of drugs for type 2 diabetes to highlight the shortcomings of the evidence standards for licensing, reimbursing, and adopting new preventive drugs and suggest some solutions.

Time to curb regulatory enthusiasm for “timely market access”

Blood glucose lowering is the only benchmark used by regulatory agencies to grant market approval to antidiabetic drugs (box 1). There are more than 30 antidiabetic drugs on the market, and for most we have insufficient evidence from

randomised trials about their long term clinical benefits or harms.

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,¹⁵ encourages drug companies to develop ever increasing numbers of glucose lowering drugs. There are currently over 200 molecules in the development pipeline.^{16,17} 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.¹⁸ 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, drug withdrawals and black box warnings have increased.^{19,20} For example, the glucose lowering drug rosiglitazone was initially heralded as a breakthrough drug but was later found to increase the risk of cardiovascular adverse events and was withdrawn from European markets in 2010.^{9,21,22}

We suggest two strategies that could improve the therapeutic value of antidiabetic drugs. Both require long term data on patient centred outcomes in a timely manner to allow clinicians and patients to make informed decisions (table 1). Although both strategies carry considerable administrative and financial costs, these should be weighed against the health benefits of a future scenario in which all antidiabetic drugs used in clinical practice have demonstrable effects on clinical outcomes—the sole purpose of preventive treatment. Our proposals are relevant to other preventive drugs taken by large numbers of asymptomatic people for long periods. These strategies should be considered alongside other approaches aimed at generating and disseminating evidence for more informed patients and clinicians (box 2).

Box 1: Link between glucose control and diabetic complications*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 complications (such as neuropathy) than for macrovascular complications (such as coronary artery disease)
- This has led to the widespread acceptance of blood glucose lowering as a valid surrogate measure of diabetes related microvascular and macrovascular adverse events
- Evidence shows that levels of cholesterol and blood pressure are stronger risk factors for several macrovascular outcomes in diabetes than blood glucose levels⁴

Do antidiabetic drugs reduce the risk of complications?

- While effective in reducing the risk of microvascular complications, most of the drugs currently used have not been shown to reduce the rates of macrovascular complications in randomised trials⁵⁻⁷
- Treatment with antihypertensives or statins leads to larger reductions in cardiovascular risk than treatment with antidiabetic drugs
- Intensified glucose lowering also has a greater negative effect on quality of life than lowering cholesterol or blood pressure⁸
- Several antidiabetic drugs have been found to increase the risk of cardiovascular complications⁹⁻¹²
- The net benefits of antidiabetic drugs are generally modest and vary widely depending on individual characteristics and preferences¹³
- Evidence is growing that the harms of tightly controlling blood glucose in elderly people often outweigh the benefits, with hypoglycaemia now overtaking hyperglycaemia as a cause for hospital admission in this group¹⁴

Box 2: What can be done beyond regulation?

- Clearer dissemination of evidence to both clinicians and patients may send a market signal by rewarding drugs with better evidence through higher prescription rates
- Sustained improvement is needed in mechanisms to disseminate knowledge and critical appraisal skills to clinicians and ideally to patients
- Such efforts should be reinforced by a frank discussion with patients on the strengths and weaknesses of evidence for surrogate and clinical outcomes
- Clinical practice guidelines should prioritise communication of the benefits, risks, and harms of drugs to patients, as well as the remaining uncertainties
- Patient groups should be encouraged to prioritise their existing work on getting patients to ask for evidence
- Clinicians should be encouraged to elicit and respect patients' preferences to facilitate shared decision making

Higher evidence standards by licensing agencies

The first potential strategy is for licensing agencies to raise the evidence standards for approving new drugs.²³⁻²⁶ Licensing agencies in the United States (Food and Drug Administration) and Europe (European Medicines Agency) usually require only small trials enrolling 2000-3000 patients, and few of these patients are studied for longer than six months. These trials also rarely include the key target groups for prescription of antidiabetic drugs in everyday clinical practice—namely, elderly patients with multimorbidities.²⁷ The exclusion of such patients means that the effect of new drugs in clinical practice is not tested until after licensing. Also, pivotal trials rarely provide the necessary information about the relative benefits and harms of new versus older drugs.^{23 28}

Raising the bar at point of market entry would require firms to conduct large, active comparator trials of new drugs versus existing ones, measuring outcomes in real world populations. Under this strategy, regulators would require trials lasting longer than current phase III 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 rather than following strict protocols.²⁹ This would provide realistic and timely estimates of the comparative effectiveness of new drugs.

It is often important to have several drug options available on the market to allow clinicians and patients to choose a treatment 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.²⁸ It may,

however, deter the market entry of substantially 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.”³⁰ Among such outcomes, reduction in death is most important; others include myocardial infarction, stroke, loss of vision, renal failure, amputation, neuropathy, and erectile dysfunction.

Drug related harms also influence patient independence, function, and quality of life. Reports of clinical trials generally do not include adequate data on the timing, severity, and frequency of such harms, hindering meaningful evaluation of long term safety. Such outcomes should be routinely reported in a standardised fashion.

Since 2008, the FDA has asked drug companies to show that antidiabetic drugs do not increase cardiovascular risk before they can be granted full market approval. The upper boundary of the 95% confidence interval for the hazard ratio must be <1.3; if it is between 1.3 and 1.8, approval is conditional on postmarketing evidence. This is a major step in the right direction. But by not requiring evidence of cardiovascular benefit, the FDA may indirectly discourage companies from investing in large trials to demonstrate benefit.³¹ The regulatory agencies also rarely follow up companies that have agreed to do postlicensing studies of cardiovascular safety.³² Requiring evidence of cardiovascular safety before approval would ensure that new drugs with uncertain safety do not become widely used. Research has shown that it is difficult to shift established

prescribing patterns, even when new data from well publicised studies become available.³³

Drug companies often contend that having to prove cardiovascular benefit would set an unreasonably high hurdle for the development of new therapies. However, there is no evidence that licensing agencies raising the bar for market entry of new drugs deters innovation or hinders development of antidiabetic drugs.²⁶⁻³¹ Nevertheless, licensing agencies are considering moving towards an adaptive licensing model whereby approval is based on iterative phases of evidence generation and regulatory assessment.³⁴ The premise of adaptive licensing is to tolerate greater uncertainty at the time of approval to allow for early patient access to new drugs then generating long term evidence after market entry. Although this process may be valid for severe, fast progressing, and life threatening conditions for which no successful or safe treatment exists (such as rapidly fatal malignancies), accelerated access to new drugs for type 2 diabetes is unnecessary given the number of drugs already available. 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.

Role of health technology assessment agencies

Licensing agencies are not alone in permitting antidiabetic medications to enter the market on the basis of weak evidence. Many European countries have national health technology assessment (HTA) bodies that 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.³⁵ A second potential strategy to improve the regulation of antidiabetic medications is to raise the standards of evidence required for approval by HTA agencies.

The current regulatory environment poses considerable challenges for HTA bodies, such as the UK National Institute for Health and Care Excellence (NICE). Although NICE ostensibly has higher standards of evidence (such as real world clinical data) than licensing agencies, it has limited resources and powers to enforce the conduct of new clinical studies.³⁶ In the absence of meaningful long term data, NICE often depends on mathematical models of clinical and cost effectiveness to approve or reject new medicines. Such models generally extrapolate from the short term trial findings submitted to licensing agencies, and medicines are often approved based on their effects on surrogate markers such as glycaemia and body weight despite uncertainty about the long term effects.

The second regulatory strategy would maintain the existing evidence standards within licensing agencies but ensure that new drugs 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 drug companies to hedge against uncertainties about long term clinical effects at the time of market approval.³⁷⁻³⁸ These schemes grant companies market access in return for achieving outcome targets (such as

cardiovascular benefits). Over the past few years, such schemes have become more common in Europe and the US.³⁹⁻⁴⁰

Managed entry agreements can take many forms and can be incorporated into novel regulatory pathways, including adaptive licensing. For example, a new antidiabetic drug could be “approved for randomisation,” whereby the manufacturer is required to gather more evidence about the long term cardiovascular benefits and harms of its product relative to other drugs in the same therapeutic class through low cost, head to head randomised trials.⁴¹ It is increasingly feasible to embed such simple trials in clinical practice, with follow-up data on outcomes such as myocardial infarction or death extracted from routinely collected administrative data and electronic health records.⁴² Clinicians or patients seeking a new drug that 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 standard of care comparator.

Depending on the configuration of the health service or insurance scheme, HTA agencies may choose to fully or partly reimburse the medicine while evidence is being collected. If a treatment provides the predicted benefits it can simply be upgraded to full HTA approval. If a treatment fails to meet the prespecified targets, the agency could 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 unapproved, or suggest withdrawal from the market.

Managed entry agreements, however, have limitations. Changing the coverage status of a previously reimbursed drug—or withdrawing an approved product—can pose substantial political challenges.⁴⁰ Managed entry agreements may also be operationally complex, costly, and difficult to implement. However, efforts are under way to improve the data infrastructure to collect valid information on relevant outcomes. Previous agreements have relied on observational designs to collect information on long term outcomes. Post-approval data collection for novel adaptive licensing models similarly relies on registries, cohorts, and other observational studies rather than randomised trial data.³⁴⁻⁴³ The limited experience from the US and UK suggests that without randomisation it is difficult to attribute observed differences in patient outcomes to the different drugs received.⁴⁴ Randomising patients into different drug groups would improve the validity of studies on which managed entry agreements are based.⁴⁵

Conclusion

By accepting glucose lowering as the primary yardstick by which to evaluate the effectiveness of new drugs for diabetes, regulators 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 microvascular and macrovascular outcomes.

We 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 antidiabetic drugs: do we have clear evidence that this drug improves the outcomes that matter to patients?

Contributors and sources: The authors are clinical and health policy researchers with a shared interest in the development, dissemination, and use of evidence on preventive drugs and have written several articles on this topic. BG also frequently

Key messages

- Glucose lowering drugs are allowed onto the market without adequate evidence of their effects in actual practice
- Assessment bodies such as NICE facilitate the use of such drugs without requiring subsequent production of good quality evidence
- Better regulatory strategies are needed to generate timely long term data on clinical outcomes
- This can be achieved by licensing agencies or health technology assessment bodies requiring higher standards of evidence before approval

writes in the popular press about problems in science and medicine. 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.

Competing interests: We have read and understood BMJ policy on declaration of interests and declare BG receives income from speaking and writing for lay audiences of problems in science and medicine, including those raised here.

Provenance and peer review: Not commissioned; externally peer reviewed.

- 1 Avorn J. Powerful medicines: the benefits, risks, and costs of prescription drugs. Random House, 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 the clinical utility of drugs? *Annu Rev Pharmacol Toxicol* 2015;55:169-89.
- 4 Yudkin JS, Richter B, Gale EA. Intensified glucose lowering in type 2 diabetes: time for a reappraisal. *Diabetologia* 2010;53:2079-85.
- 5 Bousageon 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:d4169.
- 6 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:d6898.
- 7 Bousageon 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:e1001204.
- 8 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;30:2478-83.
- 9 Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. *N Engl J Med* 2007;356:2457-71.
- 10 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. *Lancet* 2009;373:1765-72.
- 11 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;304:411-8.
- 12 Nissen SE, Wolski K, Topol EJ. Effect of rosiglitazone on death and major adverse cardiovascular events in patients with type 2 diabetes mellitus. *JAMA* 2005;294:2581-6.
- 13 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;174:1227-34.
- 14 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 Intern Med* 2014;174:1116-24.
- 15 Whiting DR, Guariguata L, Weil C, Shaw J. IDF diabetes atlas: global estimates of the prevalence of diabetes for 2011 and 2030. *Diabetes Res Clin Pract* 2011;94:311-21.
- 16 PhRMA. Biopharmaceutical research companies are developing 180 medicines to treat diabetes and related conditions. 2014. www.phrma.org/sites/default/files/pdf/diabetes2014.pdf.
- 17 International Federation of Pharmaceutical Manufacturers & Associations. The pharmaceutical industry and global health. 2012. www.ifpma.org/fileadmin/content/Publication/2013/IFPMA_-_Facts_And_Figures_2012_LowResSinglePage.pdf.
- 18 Philpson 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.
- 19 Carpenter D, Zucker EJ, Avorn J. Drug-review deadlines and safety problems. *N Engl J Med* 2008;358:1354-61.
- 20 Carpenter D, Chattopadhyay J, Moffitt S, Nall C. The complications of controlling agency time discretion: FDA review deadlines and postmarket drug safety. *Am J Pol Sci* 2012;56:98-114.
- 21 Cohen D. Rosiglitazone: what went wrong? *BMJ* 2010;341:c4848.
- 22 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. *Lancet* 2009;373:2125-35.
- 23 Sorenson C, Naci H, Cylus J, Mossialos E. Evidence of comparative efficacy should have a formal role in European drug approvals. *BMJ* 2011;343:d4849.
- 24 Alexander GC, O'Connor AB, Stafford RS. Enhancing prescription drug innovation and adoption. *Ann Intern Med* 2011;154:833-7.
- 25 O'Connor AB. Building comparative efficacy and tolerability into the FDA approval process. *JAMA* 2010;303:979-80.
- 26 Naci H, Cylus J, Vandroos S, Sato A, Perampaladas K. Raising the bar for market authorisation of new drugs. *BMJ* 2012;345:e4261.
- 27 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 Med* 2013;10:e1001407.
- 28 Stafford RS, Wagner TH, Lavori PW. New, but not improved? Incorporating comparative-effectiveness information into FDA labeling. *N Engl J Med* 2009;361:1230-3.
- 29 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;36:356-61.
- 30 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. *JAMA* 2000;284:1290-6.
- 31 Menon V, Lincoff AM. Cardiovascular safety evaluation in the development of new drugs for diabetes mellitus. *Circulation* 2014;129:2705-13.
- 32 Nissen SE. Setting the RECORD straight. *JAMA* 2010;303:1194-5.
- 33 Jackevicius CA, Tu JV, Ross JS, Ko DT, Carreon D, Krumholz HM. Use of fibrates in the United States and Canada. *JAMA* 2011;305:1217-24.
- 34 Eichler HG, Oye K, Baird LG, et al. Adaptive licensing: taking the next step in the evolution of drug approval. *Clin Pharmacol Ther* 2012;91:426-37.
- 35 Chalkidou K, Tunis S, Lopert R, et al. Comparative effectiveness research and evidence-based health policy: experience from four countries. *Milbank Q* 2009;87:339-67.
- 36 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. *J R Soc Med* 2007;100:453-60.
- 37 Adamski J, Godman B, Ofierska-Sujkowska G, et al. Risk sharing arrangements for pharmaceuticals: potential considerations and recommendations for European payers. *BMC Health Serv Res* 2010;10:153.
- 38 Cook JP, Vernon JA, Manning R. Pharmaceutical risk-sharing agreements. *Pharmacoeconomics* 2008;26:551-6.
- 39 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. *Soc Sci Med* 2015;124:39-47.
- 40 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 Aff (Millwood)* 2011;30:2329-37.
- 41 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.
- 42 Lauer MS, D'Agostino RB Sr. The randomized registry trial—the next disruptive technology in clinical research? *N Engl J Med* 2013;369:1579-81.
- 43 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.
- 44 Raftery J. Multiple sclerosis risk sharing scheme: a costly failure. *BMJ* 2010;340:c1672.
- 45 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;18:1-146.

Cite this as: *BMJ* 2015;351:h5260

© BMJ Publishing Group Ltd 2015

Table

Table 1 | Advantages and disadvantages of two regulatory strategies that could improve the real world therapeutic value of antidiabetic drugs

	Advantages	Disadvantages
Licensing agencies require higher evidence standards for approving new drugs	<p>Only products that offer meaningful therapeutic benefit (that is, equivalence to existing alternatives in terms of benefit and harm outcomes) allowed on market</p> <p>Generates long term evidence on comparative effectiveness in real world populations before prescribing patterns are established</p>	<p>Potential delays in market entry of new drugs</p> <p>High hurdle for development of new therapies</p>
National health technology assessment (HTA) agencies require higher evidence standards for covering and reimbursing new drugs	<p>Maintains the existing evidence standards within licensing agencies</p> <p>HTA agencies approve new drugs only when there is evidence of clear benefit on important outcomes (equivalence to existing alternatives in terms of benefit and harm outcomes)</p> <p>Managed entry agreements (eg, "approved for randomisation") ensure patient access to new drugs while evidence is generated</p>	<p>Managed entry agreements are difficult to administer because of challenges of generating evidence in clinical practice, particularly for outcomes that are not routinely collected in electronic records</p> <p>Once new evidence is generated, changing the coverage status of a previously reimbursed drug, or withdrawing an approved product, is politically challenging</p>