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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

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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⇓). 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).

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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 levels[4]

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 trials[5-7]
- 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 pressure[8]
- Several antidiabetic drugs have been found to increase the risk of cardiovascular complications[5 9-12]
- The net benefits of antidiabetic drugs are generally modest and vary widely depending on individual characteristics and preferences[13]
- 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 group[14]

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?

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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

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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	Only products that offer meaningful therapeutic benefit (that is, equivalence to existing alternatives in terms of benefit and harm outcomes) allowed on market	Potential delays in market entry of new drugs
		High hurdle for development of new therapies
	Generates long term evidence on comparative effectiveness in real world populations before prescribing patterns are established	
National health technology assessment (HTA) agencies require higher evidence standards for covering and reimbursing new drugs	Maintains the existing evidence standards within licensing agencies	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
	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)	
	Managed entry agreements (eg, “approved for randomisation”) ensure patient access to new drugs while evidence is generated	Once new evidence is generated, changing the coverage status of a previously reimbursed drug, or withdrawing an approved product, is politically challenging