therapeutics letter
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THERAPEUTICS INITIATIVE Evidence Based Drug Therapy

Questioning the basis of approval for non-insulin glucose lowering drugs

Glucose lowering drugs are commonly prescribed in British Columbia, and 44% of adults with type 2 diabetes are receiving more than one drug (see Table). Annual spending on non-insulin glucose lowering drugs in Canada was $748 million in 2013.[1] When these drugs are taken, the underlying unproven assumption is that by lowering glucose they will prevent the complications of diabetes: premature death, myocardial infarction, stroke, amputation, neuropathy, renal failure and blindness. **This Letter documents that approval of new drugs is not based on these clinically important outcomes.**

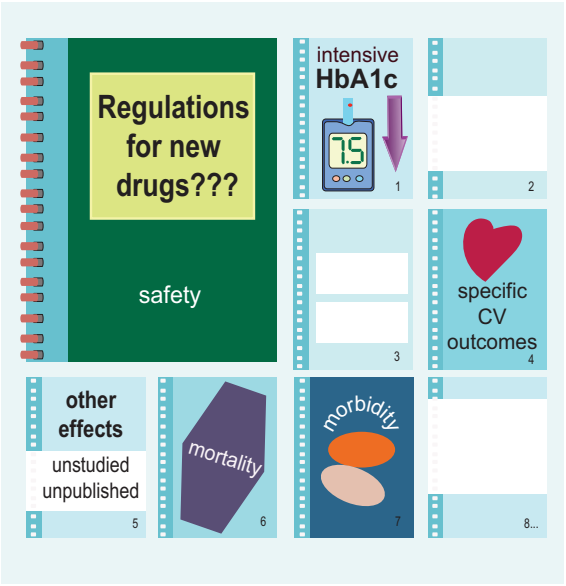
Number of patients dispensed 1 or more different glucose lowering drugs in the same calendar month		
1 drug	119,067 patients	55.9%
2 drugs	64,969 patients	30.5%
3 drugs	23,176 patients	10.9%
≥ 4 drugs	5,865 patients	2.8%

PharmaNet medication dispensing records: 213,077 people aged 40 and older. Estimate includes all insulin and non-insulin glucose lowering products approved by Health Canada as of February 2016 and excludes people dispensed insulin only between 2010 to 2015.

How does Health Canada assess non-insulin glucose lowering drugs?

In 2007, Health Canada issued the following guidance for clinical trials in type 2 diabetes: *"Clinical practice guidelines ensure the best standard of care based on current science and consensus in the medical and scientific communities. From the regulatory perspective, they are one of the measures against which the safety of the subjects is assessed during the review of clinical trial applications."*[2] Health Canada claims that adherence to Canadian Diabetes Association (CDA) guidelines *"will contribute to the safety of subjects"* and emphasizes a recommendation for *"more aggressive management of type 2 diabetes … tailored to aim for glycemic targets as close to normal as possible, and as early as possible, with the target HbA1c attained within 6 to 12 months"*.[2]

On this basis, non-insulin glucose lowering drugs approved since 2007 include (by date of approval): sitagliptin (Januvia), saxagliptin (Onglyza), liraglutide (Victoza), exenatide (Byetta), linagliptin (Trajenta), alogliptin (Nesina), canagliflozin (Invokana), dapagliflozin (Forxiga), albiglutide (Eperzan), empagliflozin (Jardiance), dulaglutide (Trulicity) and exenatide extended-release (Bydureon).[3] Health Canada's Summary Basis of Decision website presents its interpretation of the benefits and harms of drug therapies which *"reflects the information available to Health Canada regulators at the time a decision has been rendered"*.[3,4] As an example, Health Canada states that two 26-week studies supported a judgment on the clinical efficacy of liraglutide (Victoza), based on the surrogate outcome, change in HbA1c from baseline.[4] Health Canada's safety review identified the following signals: thyroid C-cell hyperplasia, thyroid C-cell tumors (animal studies), heart rate increase, PR interval prolongation, pancreatitis, hypoglycemia, gastrointestinal adverse events, immunogenicity, and injection site reactions.[4] Health Canada approved liraglutide in 2010 noting that *"Given the uncertainty regarding human risk for MTC [medullary thyroid cancer], the rejection of this product was considered; however, the clinical benefit of Victoza® as first-in-class in Canada for the treatment of Type 2 diabetes should also be considered and deemed worthwhile to balance the unknown human risk. Although there are several classes of products currently marketed in Canada for the treatment of Type 2 diabetes, there are still many patients with Type 2 diabetes (45% in the United States) who do not achieve the HbA1c target (< 7%) indicating that there is still an unmet need for new medications."*[4]



What are the potential benefits and harms of "more aggressive management of type 2 diabetes"?

A 2013 Cochrane systematic review identified 28 randomized controlled trials (RCTs) in which

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18,717 participants were randomized to intensive glycemic control vs. 16,195 participants randomized to conventional glycemic control.[5] This review included studies commonly interpreted by contemporary guidelines as evidentiary support for glycemic targets.[6,7,8] Two RCTs contributing most of the data aimed for HbA1c targets < 7% with intensive glycemic control: ADVANCE [7] (follow-up 5 years), and ACCORD [8] (follow-up 3.5 years). The Cochrane review found that key clinical outcomes such as all-cause mortality [RR 1.00, 95%CI 0.92 to 1.08], cardiovascular mortality [RR 1.06, 95%CI 0.94 to 1.21], non-fatal stroke [RR 1.0, 95%CI 0.84 to 1.19], and end-stage renal disease [RR 0.87, 95%CI 0.71 to 1.06] were not improved by intensive glucose lowering.[5] It found marginal reductions in the risk of amputation of a lower extremity [RR 0.65, 95%CI 0.45 to 0.94; ARR 0.4%] and non-fatal myocardial infarction [RR 0.87, 95%CI 0.77 to 0.98; ARR 0.7%].[5] The Cochrane reviewers rated this evidence as inconclusive, given the risks of bias of the RCTs and the limited amount of data for most outcomes. At the same time, intensive glycemic control significantly increased serious adverse events [RR 1.06, 95%CI 1.02 to 1.10; ARI 1.4%] and severe hypoglycemia (requiring assistance from another person) [RR 2.18, 95%CI 1.53 to 3.11; ARI 3.5%].[5]

Is the current regulatory focus on cardiovascular safety rational?

In 2008, the U.S. Food and Drug Administration (FDA) convened advisors to consider the cardiovascular safety of glucose lowering drugs in people with type 2 diabetes.[9] Prior to drug approval, evidence must now be provided to regulators that excludes an 80% or higher relative increase in cardiovascular risk from a new drug (defined as cardiovascular mortality, myocardial infarction, stroke, ± hospitalization for unstable angina).[10] After licensing, a single phase 4 postmarketing trial is required to exclude a 30% or higher relative increase in risk.[10] **Evidence of cardiovascular benefit is not required for initial approval or for a drug to remain on the market.**

Phase 4 trials have been published for saxagliptin, alogliptin, sitagliptin, empagliflozin, and liraglutide. [11-15] These trials generally meet the regulatory requirement of excluding a 30% relative increase in cardiovascular risk.[11-15] Each study compares the new drug added to usual care with placebo plus usual care and allows for modification of background glucose lowering drugs over the course of the trial according to unblinded HbA1c values.[11-15] This design, the FDA notes, *"limits the ability to tease apart the beneficial and detrimental effects of the investigational agent from among those of the other needed antidiabetic agents".*[16] These trials must be interpreted cautiously considering the current uncertainty regarding the effects of standard of care on cardiovascular outcomes.[17]

Furthermore, the focus on cardiovascular safety could mean that other relevant drug effects are left unstudied. To illustrate, the CDA reports that *"Diabetes is the leading cause of blindness, end stage renal disease (ESRD) and non-traumatic amputation in Canadian adults".*[18] In 2014, after failing its first review cycle, Health Canada approved canagliflozin (Invokana) on the basis that it lowered HbA1c despite having identified that the drug increased non-traumatic amputation: *"an apparent observed risk attributable to Invokana treatment of approximately one case per 480 patients treated for one year."*[19]

Conclusions

- Widely prescribed glucose lowering drugs for people with type 2 diabetes have been approved in Canada without evidence that they reduce mortality or major morbidity.
- The best available evidence does not support Health Canada's assertion that intensive glucose lowering in persons with type 2 diabetes "will contribute to the safety of subjects".
- **The current regulatory framework for glucose lowering drugs that bases benefit on lowering HbA1c and bases harms on not increasing specific cardiovascular outcomes requires rethinking.**

RR = risk ratio; 95% CI = 95% confidence interval;
ARR = absolute risk reduction; ARI = absolute risk increase.

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For a complete list of references go to: **www.ti.ubc.ca/letter100**

The draft of this Therapeutics Letter was submitted for review to 65 experts and primary care physicians in order to correct any inaccuracies and to ensure that the information is concise and relevant to clinicians.

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