

## Effect of Prepublication Results on Trends in Prescribing of Antihypertensive Medication

### Impact of the ALTITUDE (Aliskiren Trial in Type 2 Diabetes Using Cardio-Renal Disease Endpoints) Trial on Aliskiren Prescribing

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Although published randomized trial evidence can reduce prescribing of less efficacious or potentially harmful medications,<sup>1,2</sup> prepublication alerts are often released before the clinical trial results are published. It is unknown whether prepublication alerts can effectively impact population-based prescribing of medications by both primary care physicians and specialists. In this study, we explored the trends in prescribing of aliskiren, the first orally active direct renin inhibitor, in relation to drug policy decisions, prepublication alerts, and availability of evidence from randomized controlled trials.

#### Chronology of Aliskiren Prescribing in Ontario

Aliskiren was approved by the Food and Drug Administration as an antihypertensive agent in 2007<sup>3</sup> and received a notice of compliance by Health Canada in November 2007 for the treatment of hypertension.<sup>4</sup> Before listing aliskiren on the Ontario Drug Benefit (ODB) formulary, it was reviewed by the Canadian Agency for Drugs and Technology in Health (a national expert panel) and the Committee to Evaluate Drugs (a provincial expert panel), who identified the absence of long-term studies, insufficient safety data, and lack of evidence supporting a reduction in clinically important outcomes, such as stroke, myocardial infarction, and chronic kidney disease.<sup>5,6</sup> The drug was ultimately approved for listing on the Ontario provincial pharmacare formulary in December 2008, for use in patients with hypertension who have not achieved adequate blood pressure reduction with the combination of a thiazide-diuretic with either an angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker.<sup>7</sup> It is estimated that 15% to 20% of hypertensive people have uncontrolled blood pressure despite being treated with this combination of antihypertensive medications.<sup>8,9</sup>

A large postmarketing trial, ALTITUDE (Aliskiren Trial in Type 2 Diabetes Using Cardio-Renal Disease Endpoints), was initiated October 2007 and terminated early, after interim analysis showed increased frequency of nonfatal strokes, serious renal complications, hyperkalemia, and

hypotension in patients treated with aliskiren.<sup>10</sup> The manufacturer (Novartis Pharmaceuticals Canada, Inc) announced the trial termination in the media in December 2011, and Health Canada immediately informed the public that it was reviewing the safety of aliskiren. In January 2012, Health Canada (in conjunction with the manufacturer) announced warnings to health professionals and to the public about aliskiren safety. In June 2012, the drug labels were updated with the precautions and contraindications.<sup>11</sup> The Food and Drug Administration announced a warning about aliskiren and updated its drug label in April 2012. The final results of ALTITUDE were published nearly 1 year after its termination,<sup>10</sup> and the drug was delisted from the ODB formulary in the same month, December 2012.<sup>12</sup> Table includes important dates in the history of aliskiren.

#### Methods and Results

In a retrospective study of linked administrative databases, we identified all aliskiren prescriptions dispensed to hypertensive Ontario residents aged  $\geq 66$  years from April 1, 2007, to March 30, 2013, using the ODB pharmacare database. The ODB covers all prescription drugs on the formulary for Ontario residents aged  $\geq 65$  years. Hypertensive patients were identified using a previously validated database, the Ontario Hypertension database.<sup>13</sup> We determined the rate of aliskiren prescriptions (per 100 000 hypertensive senior residents of Ontario) dispensed each month during the study period, overall and by specialty of prescribing physician. A time series intervention analysis with gradual step asymptoting to a new level was used to model the monthly data and determine the impact of ALTITUDE termination on aliskiren prescribing rates.<sup>14,15</sup> We used an ARIMA time series model testing for a significant change in prescribing rate after the shock.<sup>14,15</sup> Time series analysis was performed using SAS version 9.4 (SAS Institute Inc, Cary, NC). Ethical approval for this study was obtained via the Research Ethics Board of Sunnybrook Health Sciences Center.

Between December 2008, and March 2013, a total of 321 687 aliskiren prescriptions were dispensed to 26 002

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**Table. Events and Dates in Aliskiren History**

|   |                   |
|---|-------------------|
| Approval by FDA                         | March 5, 2007     |
| Notice of compliance by Health Canada   | November 14, 2007 |
| Listing on the ODB formulary            | December 3, 2008  |
| Termination of ALTITUDE                 | December 20, 2011 |
| Health Canada recalls and safety alerts | January 23, 2012  |
| FDA warnings/labels updates             | April 16, 2012    |
| Drug monograph updates in Canada        | June 4, 2012      |
| Publication of ALTITUDE                 | December 6, 2012  |
| Delisting from the ODB                  | December 21, 2012 |

ALTITUDE indicates ALiskiren Trial In Type 2 Diabetes Using cardio-renal Disease Endpoints; FDA, Food and Drug Administration; and ODB, Ontario Drug Benefit.

elderly hypertensive residents of Ontario. Prescribing trends are shown in Figure (A). The monthly rate of aliskiren prescriptions gradually increased throughout the first 3 years of its availability, from 56/100 000 in December 2008, to a peak of 872/100 000 in December 2011. However, there was a substantial drop in the monthly rate of prescriptions after December 2011 ( $P < 0.001$ ). In January 2012, the month following the termination of the ALTITUDE trial, the rate dropped to 725/100 000 (representing a 16.9% drop from the December rate), then to 465/100 000 in February (46.7% drop from the December rate) and continued to fall steeply throughout 2012 and until the end of the study period, where it reached 114/100 000 in March 2013 (86.9% drop from December prescribing rate).

As shown in Figure (B), family physicians prescribed the majority (84.1%) of prescriptions, followed by cardiologists (5.6%), nephrologists (4.3%), and general internists (2.8%). The remaining 3.2% of aliskiren prescriptions was prescribed by other physicians from different specialties, with small numbers in each specialty group (data not shown). Aliskiren prescribing by all specialties followed the same trend. There was a gradual increase throughout the first 3 years after initial drug listing on the formulary, followed by a sudden, steep fall after December 2011. The decline in prescription rates from December 2011 to June 2012 (when drug monographs were updated) by physician type was as follows: 68% decrease in prescribing rates by family physicians (from 750 to 240 per 100 000 population), 63% decrease in prescribing rates by cardiologists (from 46 to 17 per 100 000), 81% decrease in prescribing rates by nephrologists (from 32 to 6 per 100 000), and 80% decrease in prescribing rates by general internists (from 20 to 4 per 100 000). The drops in monthly prescription rates after the intervention were statistically significant for family physicians and all 3 specialties (all  $P < 0.001$ ).

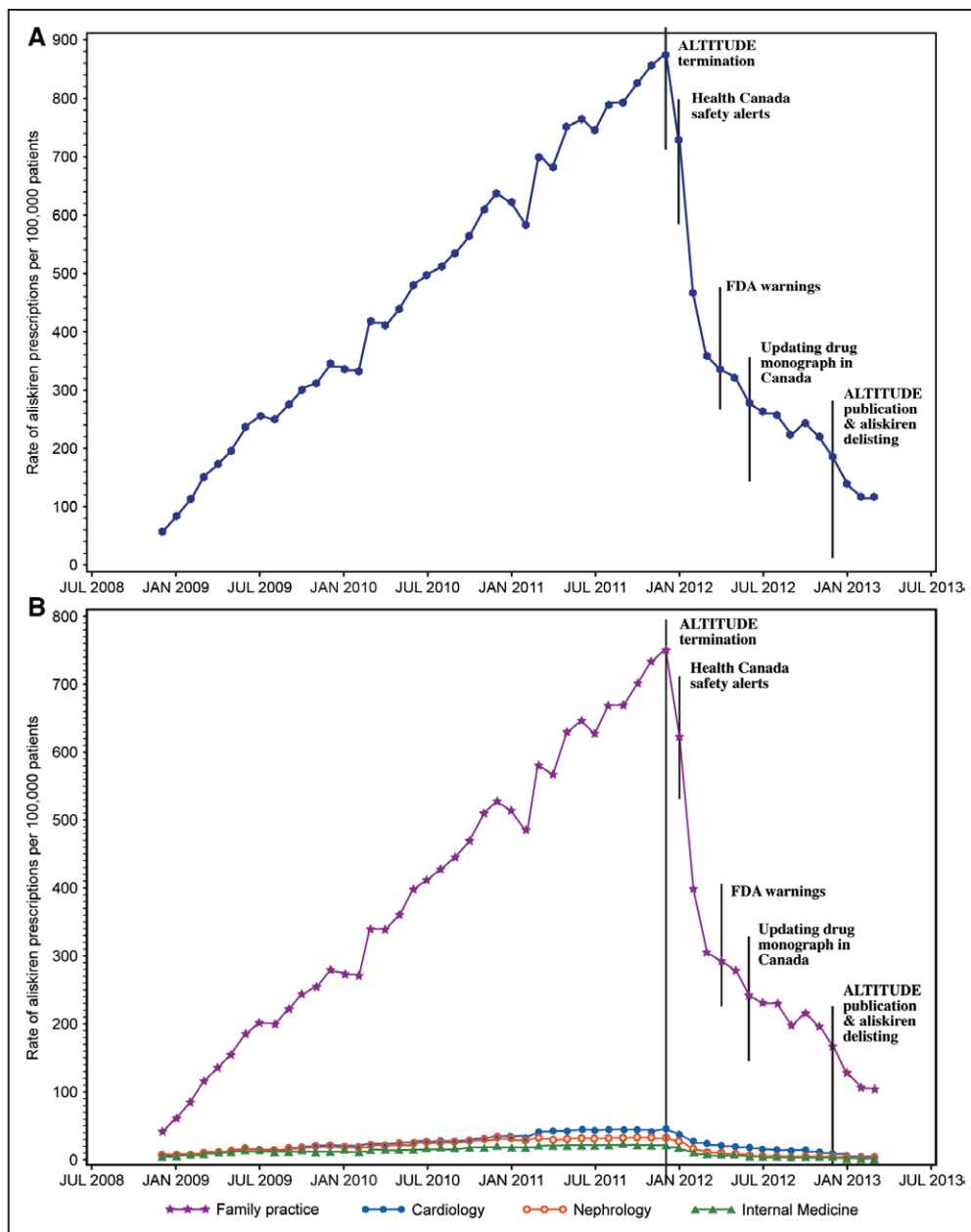
### Comment

Our analysis shows that both primary care and specialist physicians prescribed aliskiren after it was listed on the ODB formulary, despite the absence of published evidence concerning its efficacy with respect to clinically important outcomes. After the addition of aliskiren to the ODB formulary, physicians showed a tendency to prescribe this new drug to elderly

patients when large postmarketing trials were still ongoing, and data on long-term safety and effectiveness was insufficient. However, there was a rapid fall in prescriptions after prepublication alerts of safety concerns released by regulators, which was found to be statistically significant in time series analysis. This fall in prescriptions suggests that there was successful transmission of early information on potential harm from randomized controlled trials into practice. Although previous studies have shown that publication of high-profile clinical trials impacts drug prescribing,<sup>1,2</sup> this is the first analysis, of which we are aware, that demonstrates the effect of prepublication alerts on prescribing trends. A change in health policy—specifically, delisting of the drug occurred long after the rapid correction in prescribing, suggesting that changes in drug policy were slower to respond than translation of randomized clinical trial evidence.

Our analysis has several implications. First, the willingness of physicians to prescribe new drugs before published evidence, despite the availability of many other alternatives with well-established safety profile, suggests the need for interventions to increase physicians' awareness about non-evidence-based prescribing. Because of the large number of primary care providers, who represented the majority of aliskiren prescribers, interventions aimed to improve prescribing in primary care may have been beneficial. Second, regulatory agencies that approve drugs for drug-funding programs should consider this potential for non-evidence-based prescribing. Consequently, approving drugs without attaching a limitation to access or without a plan for monitoring is cautioned. Finally, the rapid decline of prescriptions after prepublication alerts and safety warnings suggests that physicians responded to early evidence that was well publicized in the professional media. Thus, in the case of aliskiren, there was ultimately successful translation of evidence into practice.

Our study has some limitations worthy of comment. Prescription data from the ODB database is limited to patients who are  $\geq 65$  years of age, and thus, we could not examine prescriptions written for younger patients. In addition, the ODB database tracks claims of prescriptions that were actually dispensed to patients but is not able to track all prescriptions written by physicians. The temporal trend analysis could not establish causality between the events related to aliskiren (eg, trial termination, regulatory initiatives) and the prescribing trends. After ALTITUDE, the ASTRONAUT (Aliskiren Trial on Acute Heart Failure Outcomes)<sup>16</sup> and AQUARIUS (Aliskiren Quantitative Atherosclerosis Regression Intravascular Ultrasound Study)<sup>17</sup> trials were presented and published, again demonstrating no benefit of aliskiren on clinical end points. Because these latter trials were presented and published after our study period, we were unable to determine their impact. Other trials of aliskiren examined blood pressure reduction end points, but they were not designed for outcomes evaluation, and therefore, these were not included.<sup>18,19</sup> Finally, although we did not examine the impact of national guidelines, it is unlikely that there was any substantive impact because there were no recommendations for or against the use of aliskiren in the Canadian Hypertension Education Program guidelines published between 2009 and 2013.<sup>20</sup> Additionally, other international guidelines (including the American Society



**Figure.** Trends in aliskiren prescribing (A) overall and (B) by physicians' specialties.

of Hypertension and International Society of Hypertension<sup>21</sup> and the Eighth Joint National Committee<sup>22</sup>) were released later in 2013, after our study period had ended.

### Conclusions

Despite the rapid adoption of new drug prescribing by physicians, prepublication alerts of evidence and actions by health regulators can have a considerable impact on prescription practices.

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## Disclosures

None.

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