Pharmacist Intervention for Glycemic Control in the Community (The RxING study)

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Complete List of Authors:	Al Hamarneh, Yazid; University of Alberta, Medicine Charrois, Theresa; Curtin University, Pharmacy Lewanczuk, Richard; University of Alberta, Medicine Tsuyuki, Ross; University of Alberta, Faculty of Medicine and Dentistry
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Pharmacist Intervention for Glycemic Control in the Community (The RxING study)

Yazid N Al Hamarneh, PhD, EPICORE Centre, Division of Cardiology, Department of Medicine, University of Alberta

Theresa Charrois, MSc, School of Pharmacy, Curtin University

Richard Lewanczuk, MD, PhD, Department of Medicine, University of Alberta

Ross T Tsuyuki, PharmD, MSc, Professor of Medicine and Director, EPICORE Centre, Division of Cardiology, Department of Medicine, University of Alberta (Corresponding author)

EPICORE Centre

220 College Plaza

University of Alberta

Edmonton, Alberta

T6G 2C8

Tel: 780-492-8526

Fax: 780-492-6059

ross.tsuyuki@ualberta.ca

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Abstract

Objective: To determine the effect of a community pharmacist prescribing intervention on glycemic control in patients with poorly controlled type 2 diabetes.

Design: Pragmatic, before-after design

Setting: 12 community pharmacies in Alberta, Canada.

Participants: Type 2 diabetes receiving oral hypoglycemic medications and with HbA1c of 7.5-11%

Intervention: Pharmacists systematically identified potential candidates by inviting patients with Type 2 diabetes to test their HbA1c using validated point of care technology (DCA Vantage®). Pharmacists prescribed 10 units of insulin glargine at bedtime, adjusted by increments of 1 unit daily to achieve a morning fasting glucose of ≤5.5mmol/L. The patients were followed at 2, 4, 8, 14, 20, and 26 weeks.

Primary outcome: Change in HbA1c from baseline to week 26.

Secondary outcomes: Proportion of patients achieving target HbA1c, changes in oral hypoglycemic agents, persistence on insulin glargine, number of insulin dosage adjustments per patient and number of hypoglycemic episodes.

Results: We screened 365 patients of which 111 were eligible. Of those, 100 (90%) were enrolled in the study; all 11 patients who did not consent refused to use insulin.

Average age was 64 years (standard deviation (SD) 10.4), while average diabetes duration was 10.2 years (SD 7). HbA1c was reduced from 9.1% (SD 1) at baseline to 7.3% (SD 0.9) a change of 1.8% ($p < 0.001$). Fasting plasma glucose was reduced from 11 mmol/l (SD 3.3) to 6.9 mmol/l (SD 1.8), a change of 4.1 mmol/l ($p=0.007$). Fifty one percent of the patients achieved the target HbA1c of ≤ 7% at the end of the study.

Conclusion: This is the first completed study of independent prescribing by pharmacists. Our results showed similar improvements in glycemic control as previous physician-led studies. RxING provides further evidence for the benefit of pharmacist care in diabetes.

Trial registration: clinicaltrials.gov; Identifier: NCT01335763

Article summary

Article focus:

To determine the effect of a community pharmacist prescribing intervention on glycemic control in patients with poorly controlled type 2 diabetes.

Key Messages:

- Community pharmacist prescribing intervention on glycemic control in patients with poorly controlled type 2 diabetes reduced patients' HbA1c from 9.1% at baseline to 7.3% at 26 weeks, a change of 1.8%. While fasting plasma glucose (FPG) was reduced from 11 mmol/L at baseline to 6.9 mmol/L at 26 weeks, a change of 4.1 mmol/L
- Pharmacists can systematically identify patients with poor glycemic control, educate and support them to achieve better outcomes
- Since pharmacists see patients with diabetes frequently, we recommend getting the pharmacists more involved in delivering the care for patients with type 2 diabetes

Strengths and limitations of the study:

- This is the first study of independent prescribing by pharmacists in patients with diabetes and it demonstrates a clinically important improvement in glycemic control.
- The 26 week follow up period can be considered relatively short; it is possible that with a longer study more patients may have achieved the target HbA1c (or fewer if patients discontinued their insulin).
- We did observe a number of "hypoglycemic-type symptoms", however we were not able to confirm these as true hypoglycemia. We also have no frame of reference as patients may have experienced some of these symptoms prior to enrolling in our study. Finally,

the number of reported “hypoglycemic-type symptoms” in this study was consistent with the findings reported in the literature.

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Introduction

Currently, 347 million individuals are living with diabetes worldwide (1). Approximately 90% of those individuals have type 2 diabetes (1). The number of new cases of type 2 diabetes is rapidly increasing mainly because of obesity and an ageing population (2).

Because of its chronic nature and the severe complications associated with it, diabetes carries a health and a financial burden on the affected individual and health systems (3). Poorly controlled diabetes puts patients at high risk of suffering from macrovascular and microvascular complications (4).

Type 2 diabetes is a progressive disease; it has been reported that 50% of the insulin producing capacity is lost at the time of diagnosis with an average loss rate of 5% per year afterwards (5). As a result, many patients with type 2 diabetes will eventually require the use of insulin; however, clinicians seem reluctant to start insulin (6) despite the evidence from studies such as INSIGHT, which demonstrated improved glycemic control with the addition of insulin glargine to oral hypoglycemic agents in patients with type 2 diabetes (7) as well as guidelines that recommending starting insulin immediately if the patients HbA1c is ≥ 9% (8).

Pharmacists are front line healthcare professionals who see patients with diabetes more frequently than physicians (15 times/year Vs 7 times/year) (9) and as such, could proactively and systematically identify patients with poorly controlled type 2 diabetes in a broad-based public health approach to chronic disease management. Indeed, there is good evidence for the efficacy

of pharmacist care in diabetes (10). Moreover, the scope of practice for pharmacists is changing, allowing pharmacists to prescribe medications and order laboratory tests. As such, there is an unprecedented opportunity to identify and improve glycemic control in patients with type 2 diabetes.

The main aim of the RxING study was to determine the effect of a community pharmacist prescribing intervention on glycemic control in patients with poorly controlled type 2 diabetes.

Methods

RxING was a multicentre pragmatic before-after design trial, which was conducted in 12 community pharmacies in the province of Alberta, Canada.

We recruited adults who had physician diagnosed type 2 diabetes for at least six months and were receiving one or more oral hypoglycemic agents, had a HbA1c between 7.5% and 11%, and who were willing to sign an informed consent.

We excluded patients who were unwilling to use insulin, previously or currently using insulin, had a history of ketoacidosis, were pregnant, worked night shifts, had renal impairment (serum creatinine of ≥ 124 mmol/l for females or ≥ 133 mmol/l for males), were clinically unstable, were unwilling or unable to attend follow-up visits, or felt to be unlikely to adhere to study procedures due to cognitive limitations, severe psychiatric disorders or alcoholism.

Pharmacists systematically identified potential candidates by inviting patients with type 2 diabetes (e.g. patients on metformin) to test their HbA1c in the pharmacy using validated point of care technology (DCA Vantage®, Siemens, Tarrytown, New York, USA). If the result of the HbA1c test was high (7.5-11 %) and the patient met the other inclusion criteria for the study the patient was asked if he/she wanted to participate in the study. After providing written informed consent, the patient was enrolled in the study. If HbA1c was > 11% the patient was assessed by the study investigators, and the patient was referred to his/her physician.

Intervention: The patient was prescribed 10 units insulin glargine at bedtime, and was asked to titrate the dose by 1 unit/day to achieve a fasting plasma glucose of ≤ 5.5 mmol/L (7, 11). The intervention also included patient education regarding insulin use, dose titration and self monitoring. Patients contacted the pharmacist when they reached a fasting plasma glucose of 6 mmol/L. All patients remained on their previously prescribed oral hypoglycemic agent(s). Adjustments were made at the discretion of the treating pharmacist. The patient's family physician received a letter from the pharmacist to inform him/her that the patient was participating in the study.

Follow-up: Patients were followed at 2, 4, 8, 14, 20, and 26 weeks to provide ongoing care, check adherence to the insulin regimen, fasting blood sugars (measured by the patient), insulin dose and titration and adverse events. HbA1c was measured at weeks 14 and 26 using the same technique used at baseline. Family physicians were kept informed of patient's progress and any medication change after each visit.

The primary outcome measure was the change in HbA1c from baseline to week 26. Secondary outcomes included: Proportion of patients achieving target HbA1c (defined as HbA1c ≤7.0%), changes in oral hypoglycemic agents, persistence on insulin glargine (% still taking insulin at the end of follow-up), number of insulin dosage adjustments per patient, number of hypoglycemic episodes.

With a sample size of 80 patients and the following assumptions: a standard deviation of 1.1 and a 2 sided alpha of 0.05 (7) we calculated 90% power to detect a mean decrease in HbA1c of 0.4%. Since this a pragmatic, practice-based trial, the sample size was inflated to 100 to account for possible losses to follow-up.

The level of significance was set at 0.05. All analyses were done on intention to treat basis. Missing data were imputed using a last value carried forward strategy. The primary outcome was analyzed using t-test after adjusting for the patients' demographics and clinical characteristics. The secondary outcomes were analyzed using t-test and basic frequencies after adjusting for the patients' demographics and clinical characteristics.

RxING was approved by the Health Research Ethics Board of the University of Alberta and was registered on clinicaltrials.gov (NCT01335763).

Results

We screened 356 patients with type 2 diabetes; 245 were excluded because they did not meet the HbA1c inclusion criteria. Out of the 111 eligible patients, 11 were not enrolled because they refused to use insulin, leaving 100 patients enrolled (Figure 1)

The demographic and clinical characteristics of the patients are reported in Table 1. The mean age was 64 years (Standard Deviation (SD) 10.4) and had a diabetes duration of 10.2 years (SD 7). Fifty-eight percent of the patients were male, 77% were married and 90% reported having at least high school education. Nearly half of the patients (48%) were retired, almost ninety percent (89%) were white (ethnicity was self reported) and nearly half (47%) have a government medication coverage. Around one quarter of the patients (22%) reported that they were smokers, More than half (54%) reported occasional consumption of alcohol (e.g. 1-3 drinks/week), almost half (47%) reported not using any specific diet for their diabetes, more than half (51%) reported being moderately active (exercising for 30 minutes less than 5 times per week) and more than four fifths (85%) reported living at least a mildly stressful life.

All but 1 patient was taking insulin glargine at the end of the study (he stopped his insulin before the final visit because his plasma glucose readings were “good”). At the end of the study the mean insulin glargine dose was 31.1 units (SD 18.4) with a mean of 21.1 dose adjustments (SD 18.8) per patient.

HbA1c was reduced from 9.1% (SD 1) at baseline to 7.3% (SD 0.9) at 26 weeks, a change of 1.8% (95% CI 1.4-2, p<0.001) (Figure 2). While fasting plasma glucose (FPG) was reduced from 11 mmol/L (SD 3.3) at baseline to 6.9 mmol/L (SD 1.8) at 26 weeks, a change of 4.1 mmol/L (95% CI of 3.3-5, p= 0.007) (Figure 3)

Fifty one percent of the patients achieved the target HbA1c of ≤ 7% at the end of the study. Nearly half of the patients (48%) had their oral hypoglycemic regimen altered (Table 2); the most frequent alterations were stopping sulfonylurea (46%) followed by initiating meglitinides (23%), stopping metformin (21%) and stopping thiazolidinedoine and DPP4 inhibitors (19%).

There was an apparent slight increase in the body mass index (BMI) and waist circumference between baseline and the end of the study but this increase was not statistically significant (31.6 (SD 6.3) to 32.6 (SD 6.3), p=0.29 and 106 (SD 13.8) to 107.4 (SD 12.9), p=0.5 respectively).

Hypoglycemic symptoms were reported by 54 patients. Only 2 of these episodes required medical attention; one caused a visit to the family physician while the other required a visit to the emergency department without an overnight stay. We were not able to confirm that these episodes were true hypoglycemia (we were not able to confirm blood sugars associated with these events).

Discussion

We found that a community pharmacist prescribing intervention on glycemic control in patients with poorly controlled type 2 diabetes reduced patients' HbA1c by an absolute value of 1.8% (95% CI 1.4-2, p<0.001) and improved fasting plasma glucose by 4.1 mmol/L (95% CI of 3.3-5, p= 0.007). This is the first study of independent prescribing by pharmacists in patients with diabetes and demonstrates a clinically important improvement in glycemic control.

Our findings are consistent with the findings of Gerstein and colleagues (2006) and Harris and colleagues (2008) who compared the effect of adding insulin glargine to the oral hypoglycemic regimen versus the conventional therapy where oral hypoglycemic agent doses were adjusted. They reported better glycemic control in the insulin glargine group after 26 weeks of follow up (7, 12). Our findings are also consistent with the findings of Wubben and Vivian (2008) who conducted a systematic review to assess the effectiveness of pharmacist intervention in patients with diabetes in outpatient settings. They reported additional HbA1c reduction (when compared to usual care) of 0.5% when pharmacists did not have prescribing authority and 1% when pharmacists had prescribing authority (collaborative prescribing in this case) (10).

It has been reported in the literature that the adherence rates to the insulin regimen are unsatisfactory (14); however in our study, 99% of the patients were adherent to their treatment regimen for 6 months, this can be explained by the intensive intervention provided by the pharmacist and the relatively short duration of the study.

The slight increase in BMI and waist circumference in our study is consistent with the findings of Heine and colleagues (2005) and Russell-Jones and colleagues (2009) who compared the efficacy of insulin glargine to an active diabetes treatment and reported that there was a slight increase in BMI and waist circumference in patients who used insulin glargine after 26 weeks (15, 16).

This study is not without limitations. The 26 week follow up period can be considered relatively short; it is possible that with a longer study more patients may have achieved the target HbA1c (or fewer if patients discontinued their insulin). We did observe a number of "hypoglycemic-type symptoms", however we were not able to confirm these as true hypoglycemia. We also have no frame of reference as patients may have experienced some of these symptoms prior to enrolling in our study. Finally, the number of reported "hypoglycemic-type symptoms" in this study was consistent with the findings of a meta analysis of more than 1100 diabetes patients who were using insulin glargine (17).

Our findings take the evidence for the benefits of pharmacist care in diabetes one step further. That prescribing insulin improves glycemic control in itself is perhaps not surprising; what is important is that pharmacists can systematically identify patients with poor glycemic control, educate and support patients to achieve better outcomes. Since pharmacists see patients with diabetes frequently (9), this is an attractive approach which should be implemented.

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Contributors: All the authors have made substantial contributions to the manuscript. These contributions are as the following: Al Hamarneh had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design*: Tsuyuki and Charrois. *Acquisition of data*: Tsuyuki and Al Hamarneh. *Analysis and interpretation of data*: Tsuyuki and Al Hamarneh. *Drafting of the manuscript*: Tsuyuki and Al Hamarneh. *Critical revision of the manuscript for important intellectual content*: Tsuyuki, Lewanczuk, Charrois and Al Hamarneh. *Statistical analysis*: Tsuyuki and Al Hamarneh. *Administrative, technical, and material support*: Tsuyuki, Lewanczuk, Charrois and Al Hamarneh. *Study supervision*: Tsuyuki and Lewanczuk.

Competing interests: None declared

Ethics approval: Health Research Ethics Board of the University of Alberta

Data sharing statement: All obtained data have been analysed and reported in the manuscript.

Any further queries can be resolved by contacting the authors

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Table 1 Demographic and clinical characteristics of the patients (N=100)

Characteristic	Frequency
Gender	
Male	58
Female	42
Marital status	
Single	8
Married	77
Divorced	9
Widowed	6
Education	
Grade School	10
High School	36
Some post secondary education	26
Post secondary education	28
Employment	
Caring for family	1
Working for profit/pay	36
Unemployed/looking for a job	6
Retired	48
Other	9

Self reported Ethnicity	
Aboriginal/first nation	1
White	89
South Asian	1
Oriental	4
Other	4
Declined	1
Medication coverage	
Private	29
Government	47
Out of pocket	15
Private and government	7
Private and out of pocket	2
Smoking status	
Smoker	22
Ex-smoker	41
Non-smoker	37
Alcohol consumption	
No Alcohol	43
Occasional alcohol (e.g. 1-3 drinks/week)	54
1-2 alcohol drinks per day	3

Diet	
No specific diet	47
Diabetes Diet	7
Low Sugar	44
Low Salt	33
Low Fat	28
High Fruit and Vegetables	28
Other Diet	21
Exercise	
Very active (30 minutes of activity five or more times/week)	15
Moderately active (30 minutes of activity less than five times/week)	51
No exercise	34
Stress	
No stress	15
Mild stress	27
Moderate stress	40
High stress	18

Table 2 Oral hypoglycemic use at baseline and the end of the study

Medication	Baseline (N=100)	26 weeks (N=93)
Metformin	88	78
Sulfonylurea	54	32
Meglitinides	18	29
DPP4	12	3
Thiazolidinedione	9	0

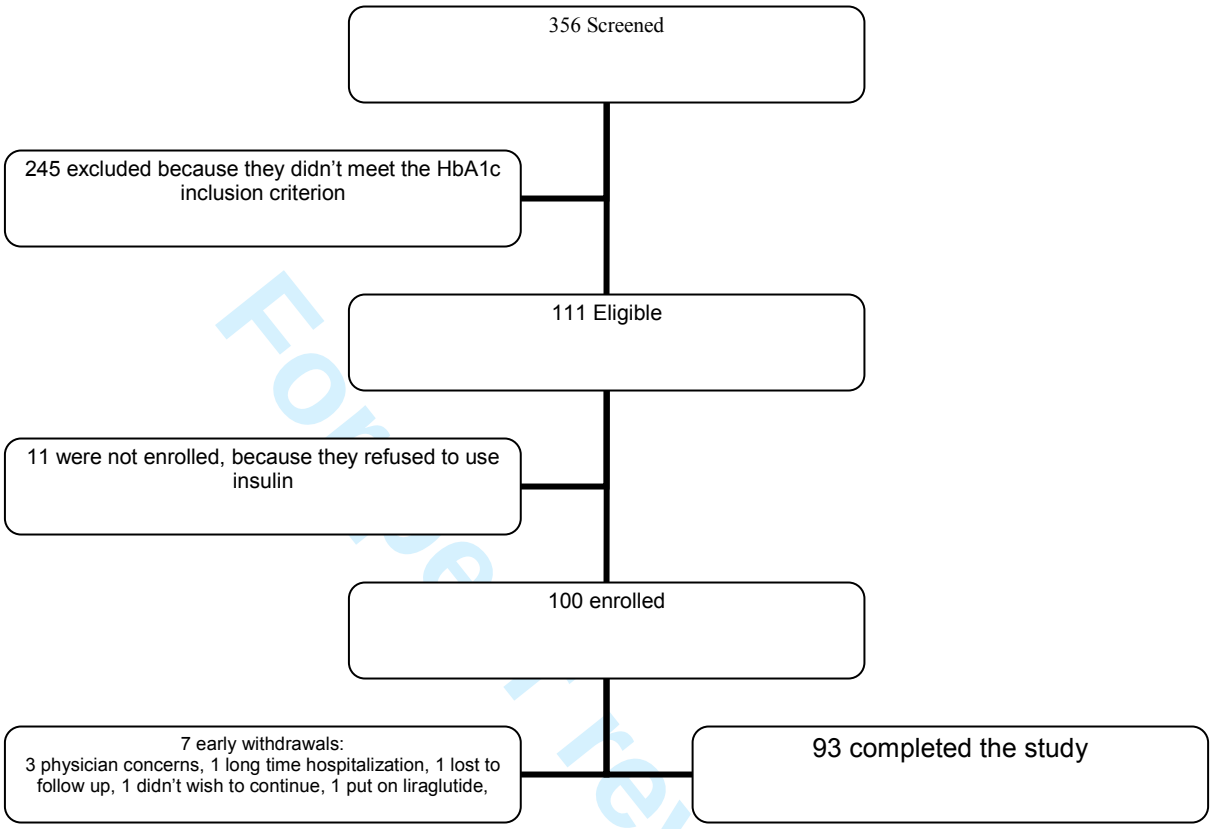

Figure 1 Patients' screening and enrollment flow chart

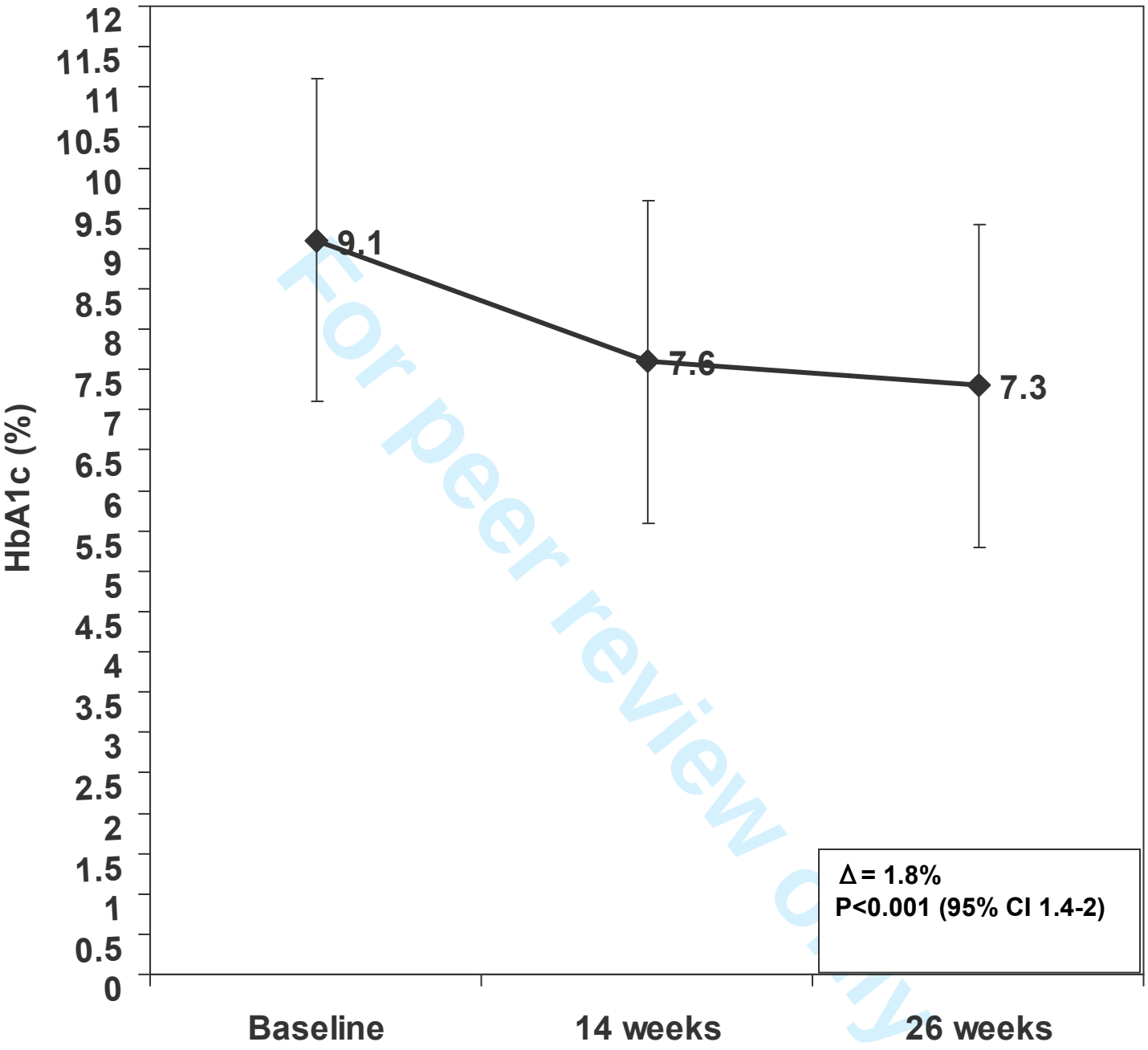

Figure 2 Intervention effect on HbA1c

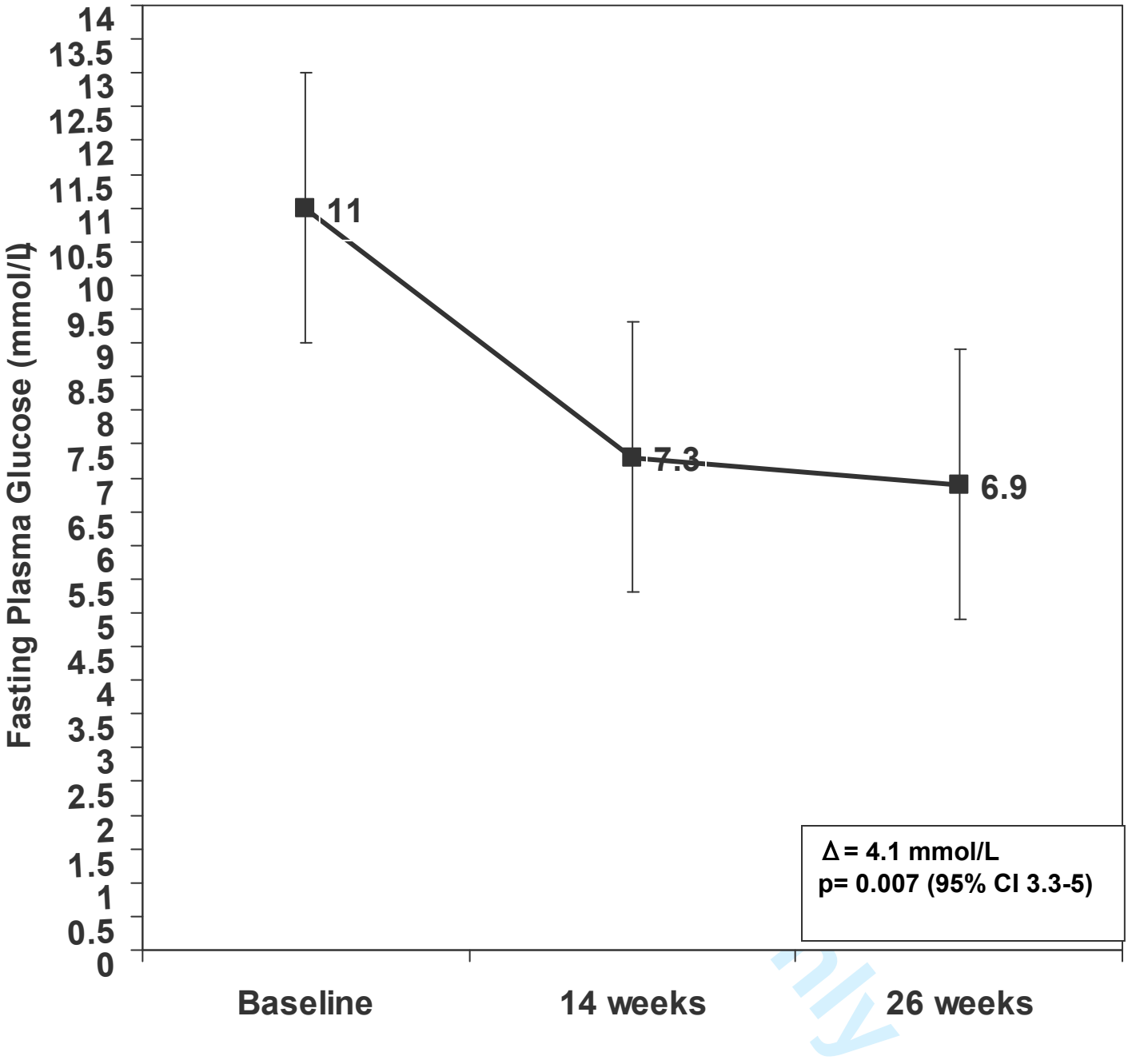

Figure 3 Intervention effect on fasting plasma glucose

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Yazid N Al Hamarneh, PhD, EPICORE Centre, Division of Cardiology, Department of Medicine, University of Alberta

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Ross T Tsuyuki, PharmD, MSc, Professor of Medicine and Director, EPICORE Centre, Division of Cardiology, Department of Medicine, University of Alberta (Corresponding author)

EPICORE Centre

220 College Plaza

University of Alberta

Edmonton, Alberta

T6G 2C8

Tel: 780-492-8526

Fax: 780-492-6059

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Intervention: Pharmacists systematically identified potential candidates by inviting patients with Type 2 diabetes to test their HbA1c using validated point of care technology (DCA Vantage®). Pharmacists prescribed 10 units of insulin glargine at bedtime, adjusted by increments of 1 unit daily to achieve a morning fasting glucose of ≤5.5mmol/L. The patients were followed at 2, 4, 8, 14, 20, and 26 weeks.

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Conclusion: This is the first completed study of independent prescribing by pharmacists. Our results showed similar improvements in glycemic control as previous physician-led studies. RxING provides further evidence for the benefit of pharmacist care in diabetes.

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- Pharmacists can systematically identify patients with poor glycemic control, educate and support them to achieve better outcomes
- Since pharmacists see patients with diabetes frequently, we recommend getting the pharmacists more involved in delivering the care for patients with type 2 diabetes

Strengths and limitations of the study:

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Introduction

Currently, 347 million individuals are living with diabetes worldwide (1). Approximately 90% of those individuals have type 2 diabetes (1). The number of new cases of type 2 diabetes is rapidly increasing mainly because of obesity and an ageing population (2).

Because of its chronic nature and the severe complications associated with it, diabetes carries a health and a financial burden on the affected individual and health systems (3). Poorly controlled diabetes puts patients at high risk of suffering from macrovascular and microvascular complications (4).

Type 2 diabetes is a progressive disease; it has been reported that 50% of the insulin producing capacity is lost at the time of diagnosis with an average loss rate of 5% per year afterwards (5). As a result, many patients with type 2 diabetes will eventually require the use of insulin; however, clinicians seem reluctant to start insulin (6) despite the evidence from studies such as INSIGHT, which demonstrated improved glycemic control with the addition of insulin glargine to oral hypoglycemic agents in patients with type 2 diabetes (7) as well as guidelines that recommending starting insulin immediately if the patients HbA1c is ≥ 9% (8).

Clinicians' reluctance to initiating insulin due to unfamiliarity with the treatment or using it as a last resort (9) plays a major role in influencing the patient's decision to commence insulin treatment regimen. It has been reported that many patients have 'psychological insulin resistance' where they are unwilling to take insulin because of certain beliefs that insulin will not

be beneficial and in some cases it may even be harmful. Personal experience and messages from different healthcare professionals can also affect the patient's decisions regarding insulin treatment regimen (6, 10).

Pharmacists are front line healthcare professionals who see patients with diabetes more frequently than physicians (15 times/year Vs 7 times/year) (11) and as such, could proactively and systematically identify patients with poorly controlled type 2 diabetes in a broad-based public health approach to chronic disease management (12). Indeed, there is good evidence for the efficacy of pharmacist care in diabetes (13). In community settings, pharmacists have demonstrated that they are capable of identifying poorly controlled patients, educate patients regarding diabetes, medications and self-monitoring of plasma glucose, provide adherence support, identify and resolve diabetes problems and complications and setting goals in order reduce the patients' HbA1c, plasma glucose and improve their quality of life and other co-morbidities (4, 12 - 16). Moreover, the scope of practice for pharmacists in Alberta is changing, allowing pharmacists to prescribe medications and order laboratory tests. As such, there is an unprecedented opportunity to identify and improve glycemic control in patients with type 2 diabetes.

The main aim of the RxING study was to determine the effect of a community pharmacist prescribing intervention on glycemic control in patients with poorly controlled type 2 diabetes.

Methods

Study design and setting

RxING was a multicentre pragmatic before-after design trial, which was conducted in 12 community pharmacies in the province of Alberta, Canada.

We chose the before-after design because we had concerns about withholding insulin from this high risk group. Those concerns were based on guidelines recommendations (8) and the evidence from studies such as INSIGHT (7).

All participating pharmacists, who were either certified diabetes educators (CDE) or preparing to be CDE, received face to face training by the study team. The training material was based on the most recent Canadian guidelines and recommendations (7,8). They also received a manual of operations to help them conduct the study.

Study participants

We recruited adults who had physician diagnosed type 2 diabetes for at least six months and were receiving one or more oral hypoglycemic agents, had a HbA1c between 7.5% and 11%, and who were willing to sign an informed consent.

We excluded patients who were unwilling to use insulin, previously or currently using insulin (confirmed by the patient's medication records), had a history of ketoacidosis (confirmed by the patient's healthcare records), were pregnant, worked night shifts, had renal impairment (serum creatinine of ≥ 124 mmol/l for females or ≥ 133 mmol/l for males) (confirmed by the patient's

healthcare records), were clinically unstable (based on the pharmacist's judgment), were unwilling or unable to attend follow-up visits, or felt to be unlikely to adhere to study procedures due to cognitive limitations (based on the pharmacist's judgment), severe psychiatric disorders or alcoholism (confirmed by the patient's healthcare records).

Recruitment

Pharmacists systematically identified potential candidates from within their practice by inviting patients with type 2 diabetes (e.g., patients on metformin) to test their HbA1c in the pharmacy using validated point of care technology (DCA Vantage®, Siemens, Tarrytown, New York, USA). If the result of the HbA1c test was high (7.5-11 %) and the patient met the other inclusion criteria for the study the patient was asked if he/she wanted to participate in the study. After providing written informed consent, the patient was enrolled in the study. If HbA1c was > 11% the patient was assessed by the study investigators, and the patient was referred to his/her physician.

Intervention

The patient was prescribed 10 units insulin glargine at bedtime, and was asked to titrate the dose by 1 unit/day to achieve a fasting plasma glucose of ≤ 5.5 mmol/L (7, 17). The intervention also included patient education regarding insulin use, dose titration and self monitoring. Patients contacted the pharmacist when they reached a fasting plasma glucose of 6 mmol/L. All patients remained on their previously prescribed oral hypoglycemic agent(s). If the combination with insulin was not approved in Canada, the oral hypoglycemic agent was discontinued (e.g., thiazolidinedione). Adjustments were made at the discretion of the treating pharmacist based on

the most recent Canadian guidelines (8). The patient's family physician received a letter from the pharmacist to inform him/her that the patient was participating in the study.

Follow-up

Patients were followed at 2, 4, 8, 14, 20, and 26 weeks to provide ongoing care, check adherence to the insulin regimen, fasting blood sugars (measured by the patient), insulin dose and titration and adverse events. HbA1c was measured at weeks 14 and 26 using the same technique used at baseline. Family physicians were kept informed of patient's progress and any medication change after each visit.

Outcomes

The primary outcome measure was the change in HbA1c from baseline to week 26. Secondary outcomes included: Proportion of patients achieving target HbA1c (defined as HbA1c ≤7.0%), changes in oral hypoglycemic agents, persistence on insulin glargine (% still taking insulin at the end of follow-up), number of insulin dosage adjustments per patient, number of hypoglycemic episodes.

Sample size calculation

With a sample size of 80 patients and the following assumptions: a standard deviation of 1.1 and a 2 sided alpha of 0.05 (7) we calculated 90% power to detect a mean decrease in HbA1c of 0.4%. Since this a pragmatic, practice-based trial, the sample size was inflated to 100 to account for possible losses to follow-up.

Data analysis

The level of significance was set at 0.05. All analyses were done on intention to treat basis. Missing data were imputed using a last value carried forward strategy. The mean HbA1c between baseline and 26 weeks was compared using a paired t-test. Secondary outcomes were analyzed using paired t-tests and basic frequencies. Linear regression was used to adjust for the patients' demographics and clinical characteristics.

RxING was approved by the Health Research Ethics Board of the University of Alberta and was registered on clinicaltrials.gov (NCT01335763).

Results

We screened 356 patients with type 2 diabetes; 245 were excluded because they did not meet the HbA1c inclusion criteria. Out of the 111 eligible patients, 11 were not enrolled because they refused to use insulin, leaving 100 patients enrolled (Figure 1)

The demographic and clinical characteristics of the patients are reported in Table 1. The mean age was 64 years (Standard Deviation (SD) 10.4) and had a diabetes duration of 10.2 years (SD 7). Fifty-eight percent of the patients were male, 77% were married and 90% reported having at least high school education. Nearly half of the patients (48%) were retired, almost ninety percent (89%) were white (ethnicity was self reported) and nearly half (47%) have a government medication coverage. Around one quarter of the patients (22%) reported that they were smokers, and more than half (54%) reported occasional consumption of alcohol (e.g. 1-3 drinks/week). Nearly two thirds of the patients had elevated blood pressure (63%) and elevated cholesterol (64%) (hypertension and high cholesterol were self reported).

All but 1 patient was taking insulin glargine at the end of the study (he stopped his insulin before the final visit because his plasma glucose readings were "good"). At the end of the study the mean insulin glargine dose was 31.1 units (SD 18.4) with a mean of 21.1 dose adjustments (SD 18.8) per patient.

HbA1c was reduced from 9.1% (SD 1) at baseline to 7.3% (SD 0.9) at 26 weeks, a change of 1.8% (95% CI 1.4-2, $p<0.001$) (Figure 2). While fasting plasma glucose (FPG) was reduced from

11 mmol/L (SD 3.3) at baseline to 6.9 mmol/L (SD 1.8) at 26 weeks, a change of 4.1 mmol/L (95% CI of 3.3-5, p= 0.007) (Figure 3).

Fifty one percent of the patients achieved the target HbA1c of ≤ 7% at the end of the study. At baseline, two thirds (66%) of the patients were taking two or more medications (Table 2), the most widely used combination was metformin and gliclazide, followed metformin and glyburide and metformin and repaglinide. Nearly half of the patients (48%) had their oral hypoglycemic regimen altered (Table 3); the most frequent alterations were stopping sulfonylurea (46%) followed by initiating meglitinides (23%), stopping metformin (21%) and stopping thiazolidinedoine and DPP4 inhibitors (19%). Those alterations were made by the pharmacists who then informed the patients' family physicians.

There was an apparent slight increase in the body mass index (BMI) and waist circumference between baseline and the end of the study but this increase was not statistically significant (31.6 (SD 6.3) to 32.6 (SD 6.3), p=0.29 and 106 (SD 13.8) to 107.4 (SD 12.9), p=0.5 respectively).

Hypoglycemic-type symptoms were reported by 54 patients. Only 2 of these episodes required medical attention (one caused a visit to the family physician while the other required a visit to the emergency department without an overnight stay). We were not able to confirm that these episodes were true hypoglycemia,via blood glucose measurements, nor did we have baseline information on such symptoms .

Discussion

We found that a community pharmacist prescribing intervention in patients with poorly controlled type 2 diabetes improved patients' HbA1c by an absolute value of 1.8% (95% CI 1.4-2, p<0.001) and fasting plasma glucose by 4.1 mmol/L (95% CI of 3.3-5, p= 0.007). This is the first study of independent prescribing by pharmacists in patients with diabetes and represents a clinically important improvement in glycemic control.

Our findings are consistent with the findings of Gerstein and colleagues (2006) and Harris and colleagues (2008) who compared the effect of adding insulin glargine to the oral hypoglycemic regimen versus the conventional therapy where oral hypoglycemic agent doses were adjusted. They reported better glycemic control in the insulin glargine group after 26 weeks of follow up (7, 9). Our findings are also consistent with the findings of Wubben and Vivian (2008) who conducted a systematic review to assess the effectiveness of pharmacist intervention in patients with diabetes in outpatient settings. They reported additional HbA1c reduction (when compared to usual care) of 0.5% when pharmacists did not have prescribing authority and 1% when pharmacists had prescribing authority (collaborative prescribing in this case) (13).

It has been reported in the literature that the adherence rates to the insulin regimen are unsatisfactory (19); however in our study, 99% of the patients were adherent to their treatment regimen for 6 months, this can be explained by the intensive intervention provided by the pharmacist and the relatively short duration of the study.

The slight increase in BMI and waist circumference in our study is consistent with the findings of Heine and colleagues (2005) and Russell-Jones and colleagues (2009) who compared the efficacy of insulin glargine to an active diabetes treatment and reported that there was a slight increase in BMI and waist circumference in patients who used insulin glargine after 26 weeks (20, 21).

This study is not without limitations. The 26 week follow up period can be considered relatively short; it is possible that with a longer study more patients may have achieved the target HbA1c (or fewer if patients discontinued their insulin). Patients who were unwilling to use insulin were excluded from the study; however patients' willingness to use insulin was high in our pilot study (4) and also during the screening process. The proactive and systematic approach that we used in this study also helped in identifying patients who could benefit from insulin. We acknowledge that adding insulin to the oral hypoglycemic agent(s) regimen is one of the options which are available to improve glycemic control; however this choice was based on the insulin's efficacy and safety profile. We did observe a number of "hypoglycemic-type symptoms", however we were not able to confirm these as true hypoglycemia. We also have no frame of reference as patients may have experienced some of these symptoms prior to enrolling in our study. Finally, the number of reported "hypoglycemic-type symptoms" in this study was consistent with the findings of a meta analysis of more than 1100 diabetes patients who were using insulin glargine (22).

Our findings take the evidence for the benefits of pharmacist care in diabetes one step further. That prescribing insulin improves glycemic control in itself is perhaps not surprising; what is

important is that pharmacists can systematically identify patients with poor glycemic control, educate and support patients to achieve better outcomes. Since pharmacists see patients with diabetes frequently (11), this can be an attractive approach.

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Role of the Sponsors: The funders had no role in the design and conduct of the study; in the collection, analysis, and interpretation of the data; or in the preparation, review, or approval of the final manuscript.

Contributors: All the authors have made substantial contributions to the manuscript. These contributions are as the following: Al Hamarneh had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design*: Tsuyuki and Charrois. *Acquisition of data*: Tsuyuki and Al Hamarneh. *Analysis and interpretation of data*: Tsuyuki and Al Hamarneh. *Drafting of the*

manuscript: Tsuyuki and Al Hamarneh. *Critical revision of the manuscript for important intellectual content*: Tsuyuki, Lewanczuk, Charrois and Al Hamarneh. *Statistical analysis*: Tsuyuki and Al Hamarneh. *Administrative, technical, and material support*: Tsuyuki, Lewanczuk, Charrois and Al Hamarneh. *Study supervision*: Tsuyuki and Lewanczuk.

Competing interests: None declared

Ethics approval: Health Research Ethics Board of the University of Alberta

Data sharing statement: All obtained data have been analysed and reported in the manuscript. Any further queries can be resolved by contacting the authors

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Table 1 Demographic and clinical characteristics of the patients (N=100)

Characteristic	Frequency
Gender	
Male	58
Female	42
Marital status	
Single	8
Married	77
Divorced	9
Widowed	6
Education	
Grade School	10
High School	36
Some post secondary education	26
Post secondary education	28
Employment	
Caring for family	1
Working for profit/pay	36
Unemployed/looking for a job	6
Retired	48
Other	9

Self reported Ethnicity	
Aboriginal/first nation	1
White	89
South Asian	1
Oriental	4
Other	4
Declined	1
Medication coverage	
Private	29
Government	47
Out of pocket	15
Private and government	7
Private and out of pocket	2
Smoking status	
Smoker	22
Ex-smoker	41
Non-smoker	37
Alcohol consumption	
No Alcohol	43
Occasional alcohol (e.g. 1-3 drinks/week)	54
1-2 alcohol drinks per day	3

Self reported Hypertension	
Yes	63
No	36
Unknown	1
Self reported high cholesterol	
Yes	64
No	33
Unknown	3

Table 2 Number of oral hypoglycemic agents used by patients and Mean HbA1c

Number of oral agents	Frequency	Mean HbA1c (SD)
1	34	8.7 (0.9)
2	56	9.1 (0.9)
3	7	9.8 (1.6)
4	3	8.7 (0.7)

Table 3 Oral hypoglycemic use at baseline and the end of the study

Medication	Baseline (N=100)	26 weeks (N=93)
Metformin	88	78
Sulfonylurea	54	32
Meglitinides	18	29
DPP4	12	3
Thiazolidinedione	9	0

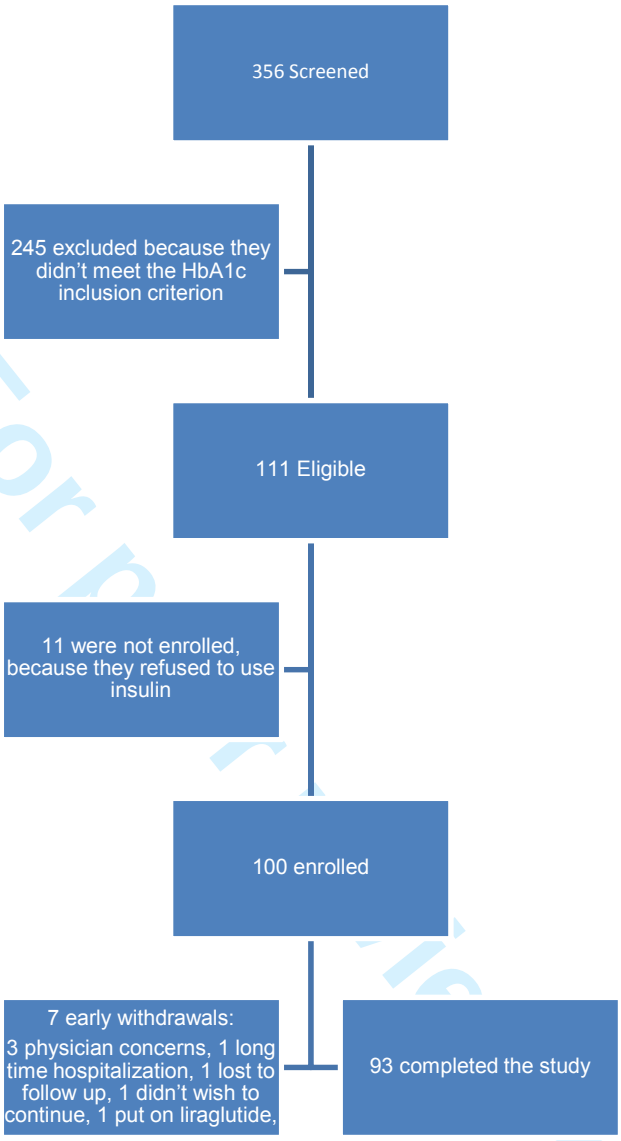


Figure 1 Patients' screening and enrollment flow chart

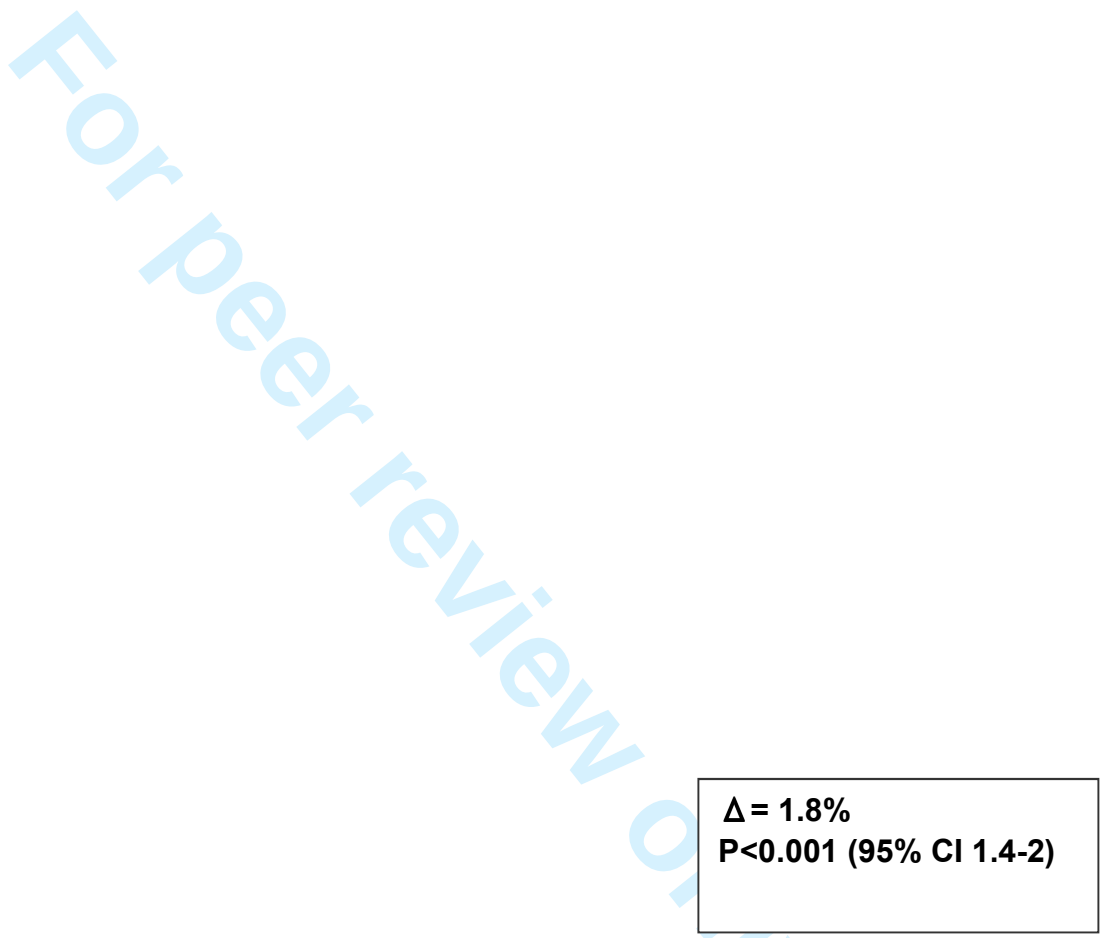
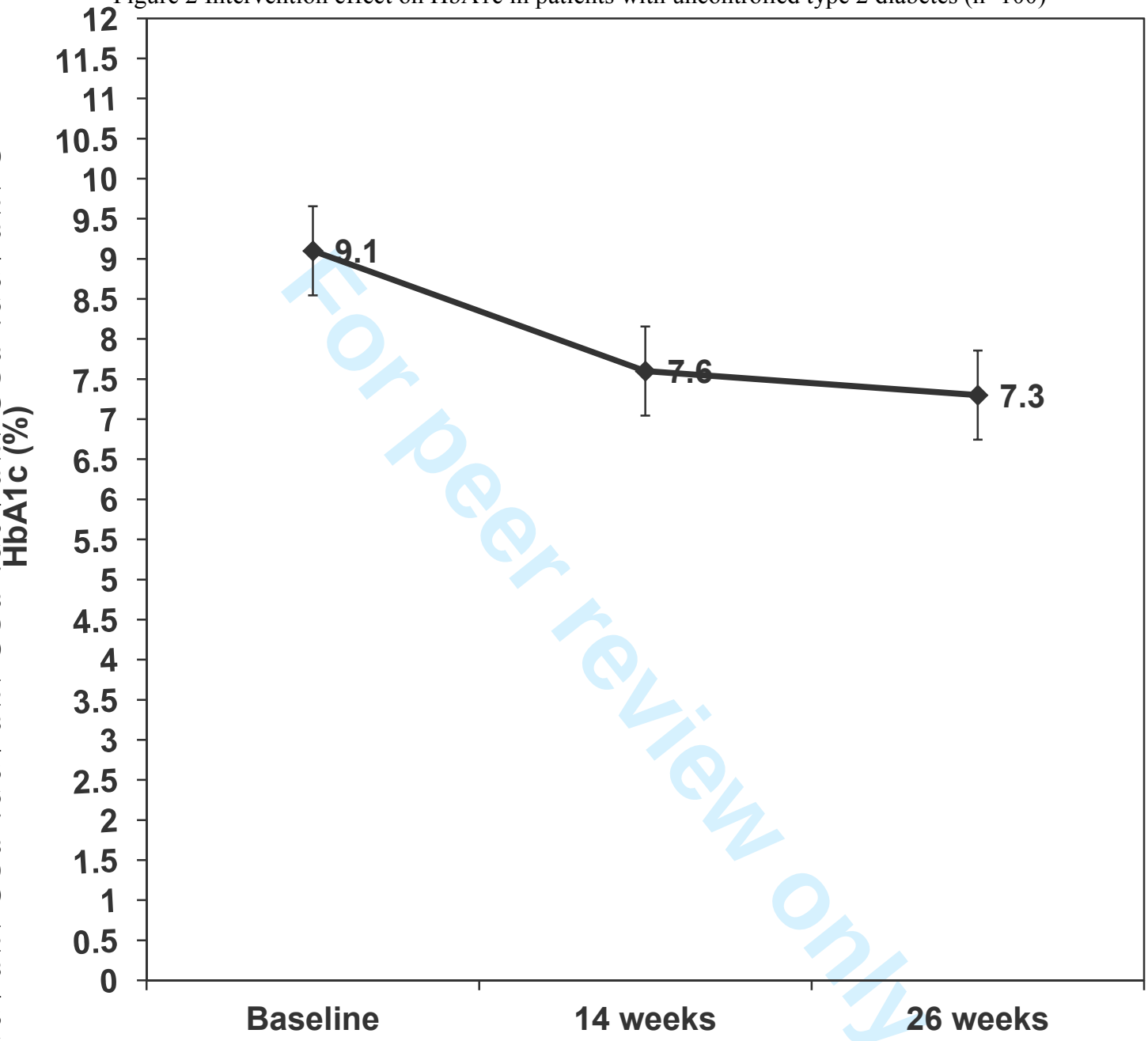


Figure 2 Intervention effect on HbA1c in patients with uncontrolled type 2 diabetes (n=100)



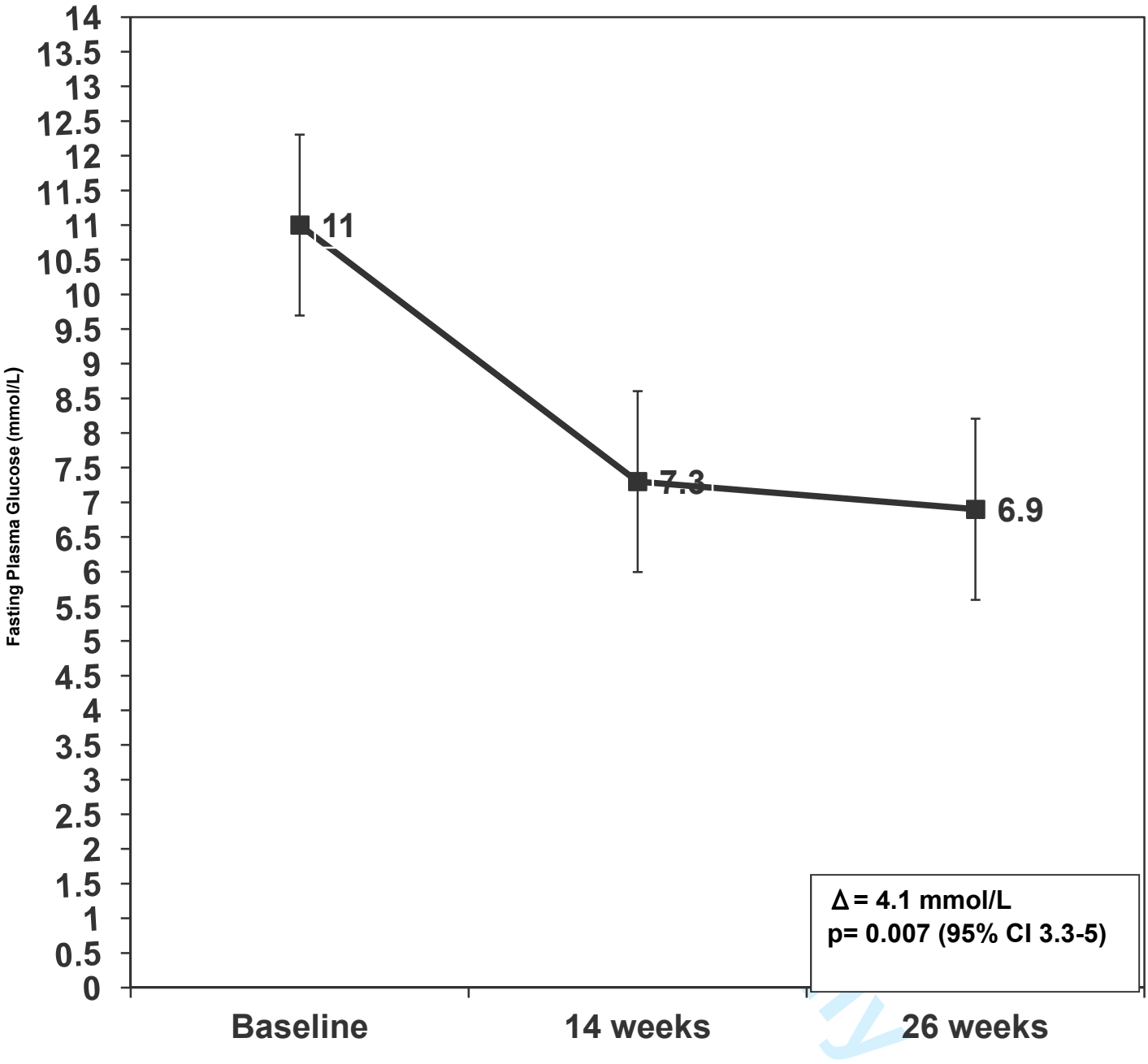


Figure 3 Intervention effect on fasting plasma glucose in patients with uncontrolled type 2 diabetes (n=100)

Pharmacist Intervention for Glycemic Control in the Community (The RxING study)

Yazid N Al Hamarneh, PhD, EPICORE Centre, Division of Cardiology, Department of Medicine, University of Alberta

Theresa Charrois, MSc, School of Pharmacy, Curtin University

Richard Lewanczuk, MD, PhD, Department of Medicine, University of Alberta

Ross T Tsuyuki, PharmD, MSc, Professor of Medicine and Director, EPICORE Centre, Division of Cardiology, Department of Medicine, University of Alberta (Corresponding author)

EPICORE Centre

220 College Plaza

University of Alberta

Edmonton, Alberta

T6G 2C8

Tel: 780-492-8526

Fax: 780-492-6059

ross.tsuyuki@ualberta.ca

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Figures: 3

Abstract

Objective: To determine the effect of a community pharmacist prescribing intervention on glycemic control in patients with poorly controlled type 2 diabetes.

Design: Pragmatic, before-after design

Setting: 12 community pharmacies in Alberta, Canada.

Participants: Type 2 diabetes receiving oral hypoglycemic medications and with HbA1c of 7.5-11%

Intervention: Pharmacists systematically identified potential candidates by inviting patients with Type 2 diabetes to test their HbA1c using validated point of care technology (DCA Vantage®). Pharmacists prescribed 10 units of insulin glargine at bedtime, adjusted by increments of 1 unit daily to achieve a morning fasting glucose of ≤5.5mmol/L. The patients were followed at 2, 4, 8, 14, 20, and 26 weeks.

Primary outcome: Change in HbA1c from baseline to week 26.

Secondary outcomes: Proportion of patients achieving target HbA1c, changes in oral hypoglycemic agents, persistence on insulin glargine, number of insulin dosage adjustments per patient and number of hypoglycemic episodes.

Results: We screened 365 patients of whom 111 were eligible. Of those, 100 (90%) were enrolled in the study; all 11 patients who did not consent refused to use insulin.

Average age was 64 years (standard deviation (SD) 10.4), while average diabetes duration was 10.2 years (SD 7). HbA1c was reduced from 9.1% (SD 1) at baseline to 7.3% (SD 0.9) a change of 1.8% (95% CI 1.4-2, p<0.001). Fasting plasma glucose was reduced from 11 mmol/l (SD 3.3) to 6.9 mmol/l (SD 1.8), a change of 4.1 mmol/l (95% CI of 3.3-5, p= 0.007). Fifty one percent of the patients achieved the target HbA1c of ≤ 7% at the end of the study.

Conclusion: This is the first completed study of independent prescribing by pharmacists. Our results showed similar improvements in glycemic control as previous physician-led studies. RxING provides further evidence for the benefit of pharmacist care in diabetes.

Trial registration: clinicaltrials.gov; Identifier: NCT01335763

Article summary

Article focus:

To determine the effect of a community pharmacist prescribing intervention on glycemic control in patients with poorly controlled type 2 diabetes.

Key Messages:

- Community pharmacist prescribing intervention on glycemic control in patients with poorly controlled type 2 diabetes reduced patients' HbA1c from 9.1% at baseline to 7.3% at 26 weeks, a change of 1.8%. While fasting plasma glucose (FPG) was reduced from 11 mmol/L at baseline to 6.9 mmol/L at 26 weeks, a change of 4.1 mmol/L
- Pharmacists can systematically identify patients with poor glycemic control, educate and support them to achieve better outcomes
- Since pharmacists see patients with diabetes frequently, we recommend getting the pharmacists more involved in delivering the care for patients with type 2 diabetes

Strengths and limitations of the study:

- This is the first study of independent prescribing by pharmacists in patients with diabetes and it demonstrates a clinically important improvement in glycemic control.
- The 26 week follow up period can be considered relatively short; it is possible that with a longer study more patients may have achieved the target HbA1c (or fewer if patients discontinued their insulin).
- We did observe a number of "hypoglycemic-type symptoms", however we were not able to confirm these as true hypoglycemia. We also have no frame of reference as patients may have experienced some of these symptoms prior to enrolling in our study. Finally,

the number of reported “hypoglycemic-type symptoms” in this study was consistent with the findings reported in the literature.

Financial acknowledgements: This work was supported by unrestricted investigator-initiated funding provided by Sanofi Canada and the testing equipments were provided by ManthaMed.

Role of the Sponsors: The funders had no role in the design and conduct of the study; in the collection, analysis, and interpretation of the data; or in the preparation, review, or approval of the manuscript.

Introduction

Currently, 347 million individuals are living with diabetes worldwide (1). Approximately 90% of those individuals have type 2 diabetes (1). The number of new cases of type 2 diabetes is rapidly increasing mainly because of obesity and an ageing population (2).

Because of its chronic nature and the severe complications associated with it, diabetes carries a health and a financial burden on the affected individual and health systems (3). Poorly controlled diabetes puts patients at high risk of suffering from macrovascular and microvascular complications (4).

Type 2 diabetes is a progressive disease; it has been reported that 50% of the insulin producing capacity is lost at the time of diagnosis with an average loss rate of 5% per year afterwards (5). As a result, many patients with type 2 diabetes will eventually require the use of insulin; however, clinicians seem reluctant to start insulin (6) despite the evidence from studies such as INSIGHT, which demonstrated improved glycemic control with the addition of insulin glargine to oral hypoglycemic agents in patients with type 2 diabetes (7) as well as guidelines that recommending starting insulin immediately if the patients HbA1c is ≥ 9% (8).

Clinicians' reluctance to initiating insulin due to unfamiliarity with the treatment or using it as a last resort (9) plays a major role in influencing the patient's decision to commence insulin treatment regimen. It has been reported that many patients have 'psychological insulin resistance' where they are unwilling to take insulin because of certain beliefs that insulin will not

be beneficial and in some cases it may even be harmful. Personal experience and messages from different healthcare professionals can also affect the patient's decisions regarding insulin treatment regimen (6, 10).

Pharmacists are front line healthcare professionals who see patients with diabetes more frequently than physicians (15 times/year Vs 7 times/year) (11) and as such, could proactively and systematically identify patients with poorly controlled type 2 diabetes in a broad-based public health approach to chronic disease management (12). Indeed, there is good evidence for the efficacy of pharmacist care in diabetes (13). In community settings, pharmacists have demonstrated that they are capable of identifying poorly controlled patients, educate patients regarding diabetes, medications and self-monitoring of plasma glucose, provide adherence support, identify and resolve diabetes problems and complications and setting goals in order reduce the patients' HbA1c, plasma glucose and improve their quality of life and other co-morbidities (4, 12 - 16). Moreover, the scope of practice for pharmacists in Alberta is changing, allowing pharmacists to prescribe medications and order laboratory tests. As such, there is an unprecedented opportunity to identify and improve glycemic control in patients with type 2 diabetes.

The main aim of the RxING study was to determine the effect of a community pharmacist prescribing intervention on glycemic control in patients with poorly controlled type 2 diabetes.

Methods

Study design and setting

RxING was a multicentre pragmatic before-after design trial, which was conducted in 12 community pharmacies in the province of Alberta, Canada.

We chose the before-after design because we had concerns about withholding insulin from this high risk group. Those concerns were based on guidelines recommendations (8) and the evidence from studies such as INSIGHT (7).

All participating pharmacists, who were either certified diabetes educators (CDE) or preparing to be CDE, received face to face training by the study team. The training material was based on the most recent Canadian guidelines and recommendations (7,8). They also received a manual of operations to help them conduct the study.

Study participants

We recruited adults -who had physician diagnosed type 2 diabetes for at least six months and were receiving one or more oral hypoglycemic agents, had a HbA1c between 7.5% and 11%, and who were willing to sign an informed consent.

We excluded patients who were unwilling to use insulin, previously or currently using insulin (confirmed by the patient's medication records), had a history of ketoacidosis (confirmed by the patient's healthcare records), were pregnant, worked night shifts, had renal impairment (serum creatinine of ≥ 124 mmol/l for females or ≥ 133 mmol/l for males) (confirmed by the patient's

healthcare records), ~~,~~ were clinically unstable (based on the pharmacist's judgment), were unwilling or unable to attend follow-up visits, or felt to be unlikely to adhere to study procedures due to cognitive limitations (based on the pharmacist's judgment), severe psychiatric disorders or alcoholism (confirmed by the patient's healthcare records).

Recruitment

Pharmacists systematically identified potential candidates from within their practice by inviting patients with type 2 diabetes (e.g., patients on metformin) to test their HbA1c in the pharmacy using validated point of care technology (DCA Vantage®, Siemens, Tarrytown, New York, USA). If the result of the HbA1c test was high (7.5-11 %) and the patient met the other inclusion criteria for the study the patient was asked if he/she wanted to participate in the study. After providing written informed consent, the patient was enrolled in the study. If HbA1c was > 11% the patient was assessed by the study investigators, and the patient was referred to his/her physician.

Intervention

The patient was prescribed 10 units insulin glargine at bedtime, and was asked to titrate the dose by 1 unit/day to achieve a fasting plasma glucose of ≤ 5.5 mmol/L (7, 17). The intervention also included patient education regarding insulin use, dose titration and self monitoring. Patients contacted the pharmacist when they reached a fasting plasma glucose of 6 mmol/L. All patients remained on their previously prescribed oral hypoglycemic agent(s). If the combination with insulin was not approved in Canada, the oral hypoglycemic agent was discontinued (e.g., thiazolidinedione). Adjustments were made at the discretion of the treating pharmacist based on

the most recent Canadian guidelines (8). The patient's family physician received a letter from the pharmacist to inform him/her that the patient was participating in the study.

Follow-up

Patients were followed at 2, 4, 8, 14, 20, and 26 weeks to provide ongoing care, check adherence to the insulin regimen, fasting blood sugars (measured by the patient), insulin dose and titration and adverse events. HbA1c was measured at weeks 14 and 26 using the same technique used at baseline. Family physicians were kept informed of patient's progress and any medication change after each visit.

Outcomes

The primary outcome measure was the change in HbA1c from baseline to week 26. Secondary outcomes included: Proportion of patients achieving target HbA1c (defined as HbA1c ≤7.0%), changes in oral hypoglycemic agents, persistence on insulin glargine (% still taking insulin at the end of follow-up), number of insulin dosage adjustments per patient, number of hypoglycemic episodes.

Sample size calculation

With a sample size of 80 patients and the following assumptions: a standard deviation of 1.1 and a 2 sided alpha of 0.05 (7) we calculated 90% power to detect a mean decrease in HbA1c of 0.4%. Since this a pragmatic, practice-based trial, the sample size was inflated to 100 to account for possible losses to follow-up.

Data analysis

The level of significance was set at 0.05. All analyses were done on intention to treat basis. Missing data were imputed using a last value carried forward strategy. The mean HbA1c between baseline and 26 weeks was compared using a paired t-test. Secondary outcomes were analyzed using paired t-tests and basic frequencies. Linear regression was used to adjust for the patients' demographics and clinical characteristics.

RxING was approved by the Health Research Ethics Board of the University of Alberta and was registered on clinicaltrials.gov (NCT01335763).

Results

We screened 356 patients with type 2 diabetes; 245 were excluded because they did not meet the HbA1c inclusion criteria. Out of the 111 eligible patients, 11 were not enrolled because they refused to use insulin, leaving 100 patients enrolled (Figure 1)

The demographic and clinical characteristics of the patients are reported in Table 1. The mean age was 64 years (Standard Deviation (SD) 10.4) and had a diabetes duration of 10.2 years (SD 7). Fifty-eight percent of the patients were male, 77% were married and 90% reported having at least high school education. Nearly half of the patients (48%) were retired, almost ninety percent (89%) were white (ethnicity was self reported) and nearly half (47%) have a government medication coverage. Around one quarter of the patients (22%) reported that they were smokers, and m~~M~~ore than half (54%) reported occasional consumption of alcohol (e.g. 1-3 drinks/week). Nearly two thirds of the patients had elevated blood pressure (63%) and elevated cholesterol (64%) (hypertension and high cholesterol were self reported).

All but 1 patient was taking insulin glargine at the end of the study (he stopped his insulin before the final visit because his plasma glucose readings were "good"). At the end of the study the mean insulin glargine dose was 31.1 units (SD 18.4) with a mean of 21.1 dose adjustments (SD 18.8) per patient.

HbA1c was reduced from 9.1% (SD 1) at baseline to 7.3% (SD 0.9) at 26 weeks, a change of 1.8% (95% CI 1.4-2, $p<0.001$) (Figure 2). While fasting plasma glucose (FPG) was reduced from

11 mmol/L (SD 3.3) at baseline to 6.9 mmol/L (SD 1.8) at 26 weeks, a change of 4.1 mmol/L (95% CI of 3.3-5, p= 0.007) (Figure 3).

Fifty one percent of the patients achieved the target HbA1c of ≤ 7% at the end of the study. At baseline, two thirds (66%) of the patients were taking two or more medications (Table 2), the most widely used combination was metformin and gliclazide, followed metformin and glyburide and metformin and repaglinide. Nearly half of the patients (48%) had their oral hypoglycemic regimen altered (Table 3); the most frequent alterations were stopping sulfonylurea (46%) followed by initiating meglitinides (23%), stopping metformin (21%) and stopping thiazolidinedoine and DPP4 inhibitors (19%). Those alterations were made by the pharmacists who then informed the patients' family physicians.

There was an apparent slight increase in the body mass index (BMI) and waist circumference between baseline and the end of the study but this increase was not statistically significant (31.6 (SD 6.3) to 32.6 (SD 6.3), p=0.29 and 106 (SD 13.8) to 107.4 (SD 12.9), p=0.5 respectively).

Hypoglycemic-type -symptoms were reported by 54 patients. Only 2 of these episodes required medical attention (one caused a visit to the family physician while the other required a visit to the emergency department without an overnight stay). We were not able to confirm that these episodes were true hypoglycemia,via blood glucose measurements, nor did we have baseline information on such symptoms .

Discussion

We found that a community pharmacist prescribing intervention in patients with poorly controlled type 2 diabetes improved patients' HbA1c by an absolute value of 1.8% (95% CI 1.4-2, p<0.001) and fasting plasma glucose by 4.1 mmol/L (95% CI of 3.3-5, p= 0.007). This is the first study of independent prescribing by pharmacists in patients with diabetes and represents a clinically important improvement in glycemic control.

Our findings are consistent with the findings of Gerstein and colleagues (2006) and Harris and colleagues (2008) who compared the effect of adding insulin glargine to the oral hypoglycemic regimen versus the conventional therapy where oral hypoglycemic agent doses were adjusted. They reported better glycemic control in the insulin glargine group after 26 weeks of follow up (7, 9). Our findings are also consistent with the findings of Wubben and Vivian (2008) who conducted a systematic review to assess the effectiveness of pharmacist intervention in patients with diabetes in outpatient settings. They reported additional HbA1c reduction (when compared to usual care) of 0.5% when pharmacists did not have prescribing authority and 1% when pharmacists had prescribing authority (collaborative prescribing in this case) (13).

It has been reported in the literature that the adherence rates to the insulin regimen are unsatisfactory (19); however in our study, 99% of the patients were adherent to their treatment regimen for 6 months, this can be explained by the intensive intervention provided by the pharmacist and the relatively short duration of the study.

The slight increase in BMI and waist circumference in our study is consistent with the findings of Heine and colleagues (2005) and Russell-Jones and colleagues (2009) who compared the efficacy of insulin glargine to an active diabetes treatment and reported that there was a slight increase in BMI and waist circumference in patients who used insulin glargine after 26 weeks (20, 21).

This study is not without limitations. The 26 week follow up period can be considered relatively short; it is possible that with a longer study more patients may have achieved the target HbA1c (or fewer if patients discontinued their insulin). Patients who were unwilling to use insulin were excluded from the study; however patients' willingness to use insulin was high in our pilot study (4) and also during the screening process. The proactive and systematic approach that we used in this study also helped in identifying patients who could benefit from insulin-. We acknowledge that adding insulin to the oral hypoglycemic agent(s) regimen is one of the options which are available to improve glycemic control; however this choice was based on the insulin's efficacy and safety profile. We did observe a number of "hypoglycemic-type symptoms", however we were not able to confirm these as true hypoglycemia. We also have no frame of reference as patients may have experienced some of these symptoms prior to enrolling in our study. Finally, the number of reported "hypoglycemic-type symptoms" in this study was consistent with the findings of a meta analysis of more than 1100 diabetes patients who were using insulin glargine (22).

Our findings take the evidence for the benefits of pharmacist care in diabetes one step further. That prescribing insulin improves glycemic control in itself is perhaps not surprising; what is

important is that pharmacists can systematically identify patients with poor glycemic control, educate and support patients to achieve better outcomes. Since pharmacists see patients with diabetes frequently (11), this can be an attractive approach.

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Contributors: All the authors have made substantial contributions to the manuscript. These contributions are as the following: Al Hamarneh had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design*: Tsuyuki and Charrois. *Acquisition of data*: Tsuyuki and Al Hamarneh. *Analysis and interpretation of data*: Tsuyuki and Al Hamarneh. *Drafting of the*

manuscript: Tsuyuki and Al Hamarneh. *Critical revision of the manuscript for important intellectual content*: Tsuyuki, Lewanczuk, Charrois and Al Hamarneh. *Statistical analysis*: Tsuyuki and Al Hamarneh. *Administrative, technical, and material support*: Tsuyuki, Lewanczuk, Charrois and Al Hamarneh. *Study supervision*: Tsuyuki and Lewanczuk.

Competing interests: None declared

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Table 1 Demographic and clinical characteristics of the patients (N=100)

Characteristic	Frequency
Gender	
Male	58
Female	42
Marital status	
Single	8
Married	77
Divorced	9
Widowed	6
Education	
Grade School	10
High School	36
Some post secondary education	26
Post secondary education	28
Employment	
Caring for family	1
Working for profit/pay	36
Unemployed/looking for a job	6
Retired	48
Other	9

Self reported Ethnicity	
Aboriginal/first nation	1
White	89
South Asian	1
Oriental	4
Other	4
Declined	1
Medication coverage	
Private	29
Government	47
Out of pocket	15
Private and government	7
Private and out of pocket	2
Smoking status	
Smoker	22
Ex-smoker	41
Non-smoker	37
Alcohol consumption	
No Alcohol	43
Occasional alcohol (e.g. 1-3 drinks/week)	54
1-2 alcohol drinks per day	3

Self reported Hypertension	
Yes	63
No	36
Unknown	1
Self reported high cholesterol	
Yes	64
No	33
Unknown	3

Table 2 Number of oral hypoglycemic agents used by patients and Mean HbA1c

Number of oral agents	Frequency	Mean HbA1c (SD)
1	34	8.7 (0.9)
2	56	9.1 (0.9)
3	7	9.8 (1.6)
4	3	8.7 (0.7)

Table 3 Oral hypoglycemic use at baseline and the end of the study

Medication	Baseline (N=100)	26 weeks (N=93)
Metformin	88	78
Sulfonylurea	54	32
Meglitinides	18	29
DPP4	12	3
Thiazolidinedione	9	0

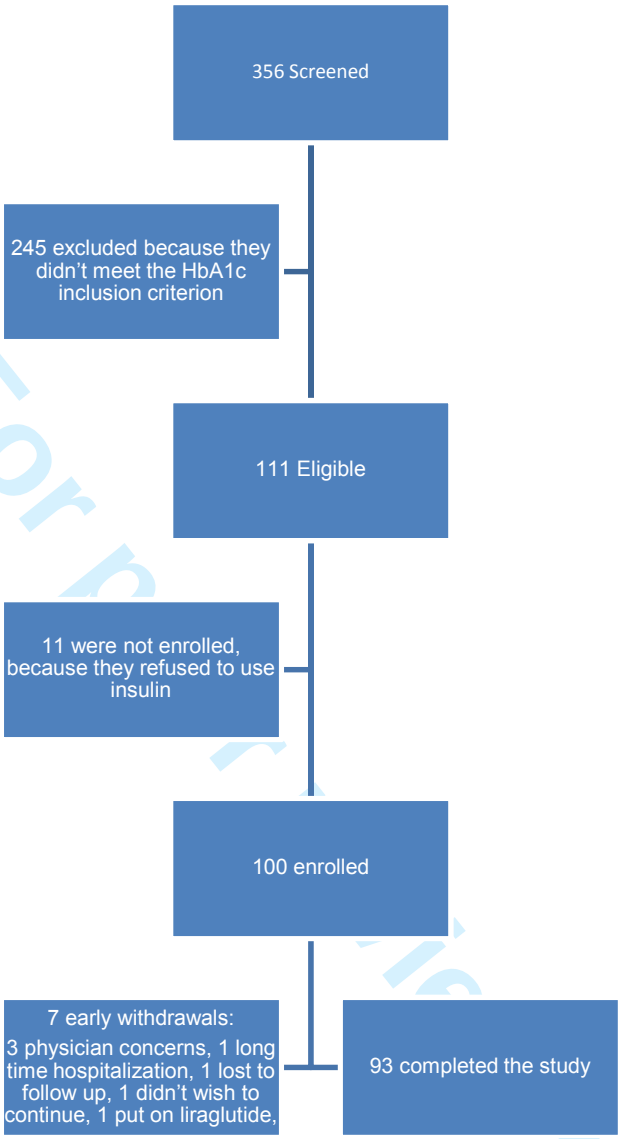

Figure 1 Patients' screening and enrollment flow chart

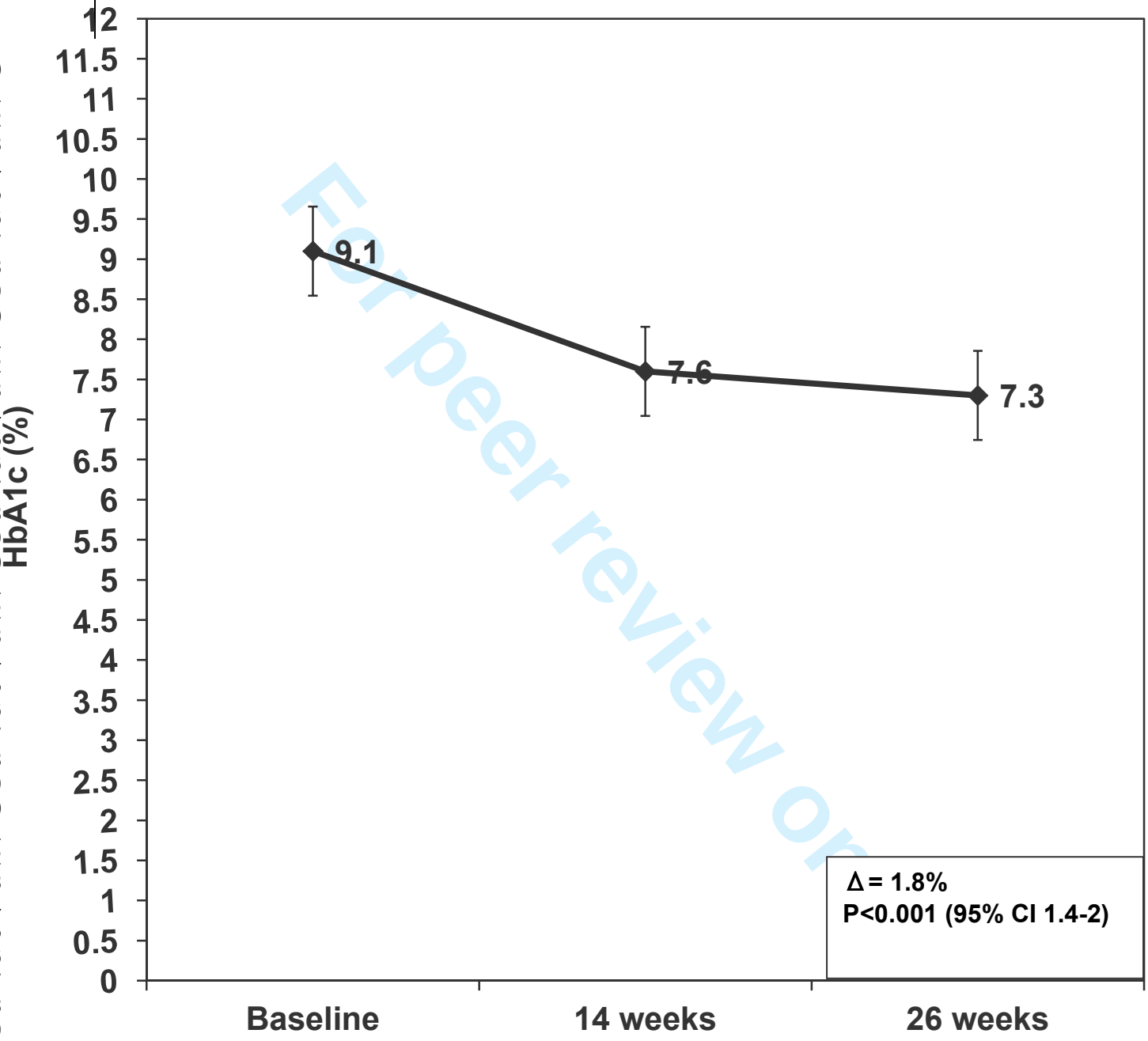

Figure 2 Intervention effect on HbA1c in patients with uncontrolled type 2 diabetes (n=100)

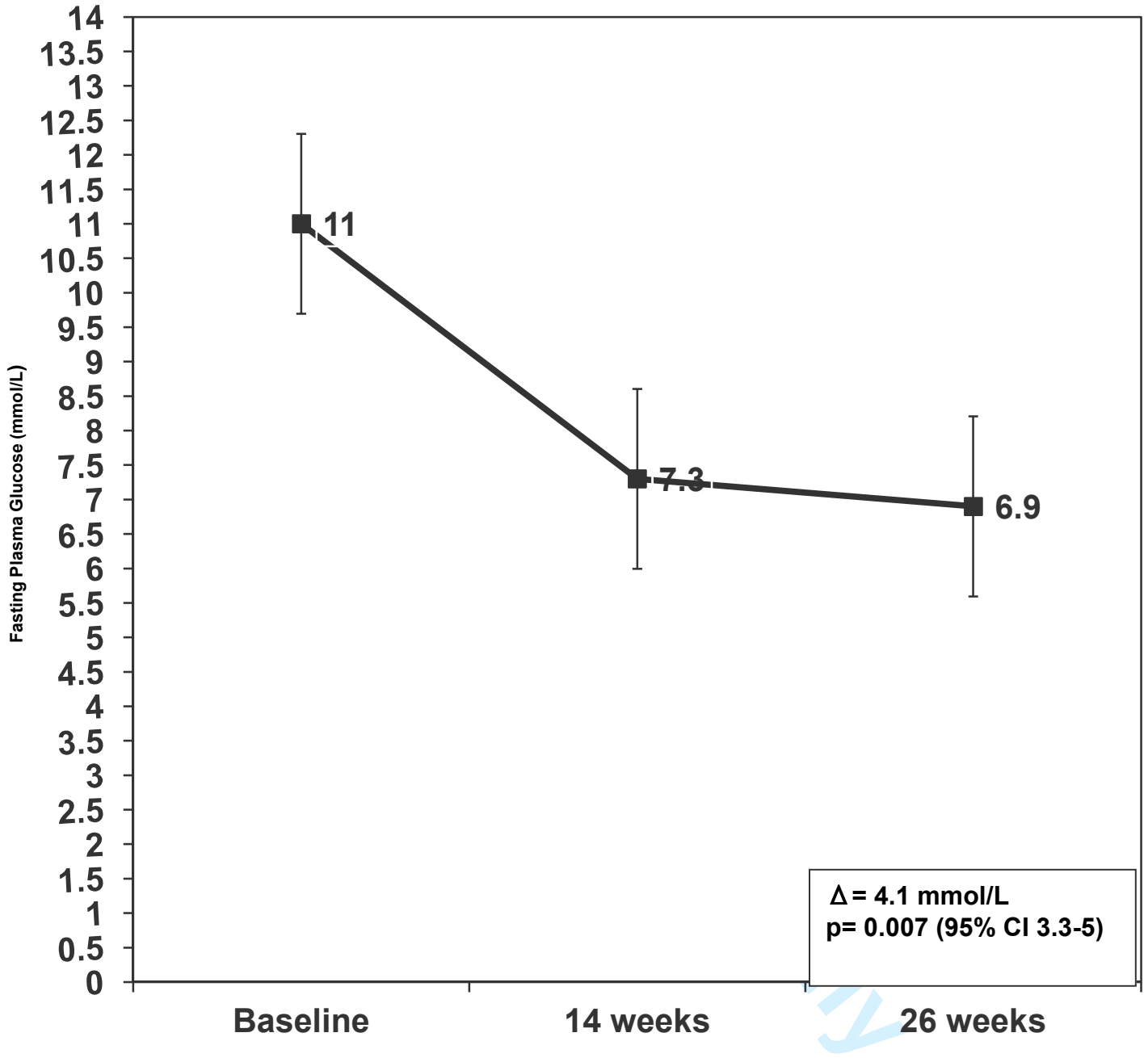

Figure 3 Intervention effect on fasting plasma glucose in patients with uncontrolled type 2 diabetes (n=100)

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Pharmacist Intervention for Glycemic Control in the Community (The RxING study)

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Pharmacist Intervention for Glycemic Control in the Community (The RxING study)

Yazid N Al Hamarneh, PhD, EPICORE Centre, Division of Cardiology, Department of Medicine, University of Alberta

Theresa Charrois, MSc, School of Pharmacy, Curtin University

Richard Lewanczuk, MD, PhD, Department of Medicine, University of Alberta

Ross T Tsuyuki, PharmD, MSc, Professor of Medicine and Director, EPICORE Centre, Division of Cardiology, Department of Medicine, University of Alberta (Corresponding author)

EPICORE Centre

220 College Plaza

University of Alberta

Edmonton, Alberta

T6G 2C8

Tel: 780-492-8526

Fax: 780-492-6059

ross.tsuyuki@ualberta.ca

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Figures: 3

Abstract

Objective: To determine the effect of a community pharmacist prescribing intervention on glycemic control in patients with poorly controlled type 2 diabetes.

Design: Pragmatic, before-after design

Setting: 12 community pharmacies in Alberta, Canada.

Participants: Type 2 diabetes receiving oral hypoglycemic medications and with HbA1c of 7.5-11%

Intervention: Pharmacists systematically identified potential candidates by inviting patients with Type 2 diabetes to test their HbA1c using validated point of care technology ~~(DCA Vantage®)~~. Pharmacists prescribed 10 units of insulin glargine at bedtime, adjusted by increments of 1 unit daily to achieve a morning fasting glucose of ≤5.5mmol/L. The patients were followed at 2, 4, 8, 14, 20, and 26 weeks.

Primary outcome: Change in HbA1c from baseline to week 26.

Secondary outcomes: Proportion of patients achieving target HbA1c, changes in oral hypoglycemic agents, quality of life and patient satisfaction, persistence on insulin glargine, number of insulin dosage adjustments per patient and number of hypoglycemic episodes.

Results: We screened 365 patients of whom 111 were eligible. Of those, 100 (90%) were enrolled in the study; all 11 patients who did not consent refused to use insulin. Average age was 64 years (~~standard deviation (~~SD~~)~~ 10.4), while average diabetes duration was 10.2 years (SD 7). HbA1c was reduced from 9.1% (SD 1) at baseline to 7.3% (SD 0.9) a change of 1.8% (95% CI 1.4-2, p<0.001). Fasting plasma glucose was reduced from 11 mmol/l (SD 3.3) to 6.9 mmol/l (SD 1.8), a change of 4.1 mmol/l (95% CI of 3.3-5, p= 0.007). Fifty one percent of the patients achieved the target HbA1c of ≤ 7% at the end of the study.

Conclusion: This is the first completed study of independent prescribing by pharmacists. Our results showed similar improvements in glycemic control as previous physician-led studies. RxING provides further evidence for the benefit of pharmacist care in diabetes.

Trial registration: clinicaltrials.gov; Identifier: NCT01335763

Article summary

Article focus:

To determine the effect of a community pharmacist prescribing intervention on glycemic control in patients with poorly controlled type 2 diabetes.

Key Messages:

- Community pharmacist prescribing intervention on glycemic control in patients with poorly controlled type 2 diabetes reduced patients' HbA1c from 9.1% at baseline to 7.3% at 26 weeks, a change of 1.8%. While fasting plasma glucose (FPG) was reduced from 11 mmol/L at baseline to 6.9 mmol/L at 26 weeks, a change of 4.1 mmol/L
- Pharmacists can systematically identify patients with poor glycemic control, educate and support them to achieve better outcomes
- Since pharmacists see patients with diabetes frequently, we recommend getting the pharmacists more involved in delivering the care for patients with type 2 diabetes

Strengths and limitations of the study:

- This is the first study of independent prescribing by pharmacists in patients with diabetes and it demonstrates a clinically important improvement in glycemic control.
- The 26 week follow up period can be considered relatively short; it is possible that with a longer study more patients may have achieved the target HbA1c (or fewer if patients discontinued their insulin).
- We did observe a number of "hypoglycemic-type symptoms", however we were not able to confirm these as true hypoglycemia. We also have no frame of reference as patients may have experienced some of these symptoms prior to enrolling in our study. Finally,

the number of reported “hypoglycemic-type symptoms” in this study was consistent with the findings reported in the literature.

Financial acknowledgements: This work was supported by unrestricted investigator-initiated funding provided by Sanofi Canada and the testing equipments were provided by ManthaMed.

Role of the Sponsors: The funders had no role in the design and conduct of the study; in the collection, analysis, and interpretation of the data; or in the preparation, review, or approval of the manuscript.

Introduction

Currently, 347 million individuals are living with diabetes worldwide (1). Approximately 90% of those individuals have type 2 diabetes (1). The number of new cases of type 2 diabetes is rapidly increasing mainly because of obesity and an ageing population (2).

Because of its chronic nature and the severe complications associated with it, diabetes carries a health and a financial burden on the affected individual and health systems (3). Poorly controlled diabetes puts patients at high risk of suffering from macrovascular and microvascular complications (4).

Type 2 diabetes is a progressive disease; it has been reported that 50% of the insulin producing capacity is lost at the time of diagnosis with an average loss rate of 5% per year afterwards (5). As a result, many patients with type 2 diabetes will eventually require the use of insulin; however, clinicians seem reluctant to start insulin (6) despite the evidence from studies such as INSIGHT, which demonstrated improved glycemic control with the addition of insulin glargine to oral hypoglycemic agents in patients with type 2 diabetes (7) as well as guidelines that recommending starting insulin immediately if the patients HbA1c is ≥ 9% (8).

Clinicians' reluctance to initiating insulin due to unfamiliarity with the treatment or using it as a last resort (9) plays a major role in influencing the patient's decision to commence insulin treatment regimen. It has been reported that many patients have 'psychological insulin resistance' where they are unwilling to take insulin because of certain beliefs that insulin will not

be beneficial and in some cases it may even be harmful. Personal experience and messages from different healthcare professionals can also affect the patient's decisions regarding insulin treatment regimen (6, 10).

Pharmacists are front line healthcare professionals who see patients with diabetes more frequently than physicians (15 times/year Vs 7 times/year) (11) and as such, could proactively and systematically identify patients with poorly controlled type 2 diabetes in a broad-based public health approach to chronic disease management (12). Indeed, there is good evidence for the efficacy of pharmacist care in diabetes (13). In community settings, pharmacists have demonstrated that they are capable of identifying poorly controlled patients, educate patients regarding diabetes, medications and self-monitoring of plasma glucose, provide adherence support, identify and resolve diabetes problems and complications and setting goals in order reduce the patients' HbA1c, plasma glucose and improve their quality of life and other co-morbidities (4, 12 - 16). Moreover, the scope of practice for pharmacists in Alberta is changing, allowing pharmacists to prescribe medications and order laboratory tests. As such, there is an unprecedented opportunity to identify and improve glycemic control in patients with type 2 diabetes.

The main aim of the RxING study was to determine the effect of a community pharmacist prescribing intervention on glycemic control in patients with poorly controlled type 2 diabetes.

Methods

Study design and setting

RxING was a multicentre pragmatic before-after design trial, which was conducted in 12 community pharmacies in the province of Alberta, Canada.

We chose the before-after design because we had concerns about withholding insulin from this high risk group. Those concerns were based on guidelines recommendations (8) and the evidence from studies such as INSIGHT (7).

All participating pharmacists, who were either certified diabetes educators (CDE) or preparing to be CDE, received face to face training by the study team. The training material was based on the most recent Canadian guidelines and recommendations (7,8). They also received a manual of operations to help them conduct the study.

Study participants

We recruited adults -who had physician diagnosed type 2 diabetes for at least six months and were receiving one or more oral hypoglycemic agents, had a HbA1c between 7.5% and 11%, and who were willing to sign an informed consent.

We excluded patients who were unwilling to use insulin, previously or currently using insulin (confirmed by the patient's medication records), had a history of ketoacidosis (confirmed by the patient's healthcare records), were pregnant, worked night shifts, had renal impairment (serum creatinine of ≥ 124 mmol/l for females or ≥ 133 mmol/l for males) (confirmed by the patient's

healthcare records), ~~,~~ were clinically unstable (based on the pharmacist's judgment), were unwilling or unable to attend follow-up visits, or felt to be unlikely to adhere to study procedures due to cognitive limitations (based on the pharmacist's judgment), severe psychiatric disorders or alcoholism (confirmed by the patient's healthcare records).

Recruitment

Pharmacists systematically identified potential candidates from within their practice by inviting patients with type 2 diabetes (e.g., patients on metformin) to test their HbA1c in the pharmacy using validated point of care technology (DCA Vantage®, Siemens, Tarrytown, New York, USA). If the result of the HbA1c test was high (7.5-11 %) and the patient met the other inclusion criteria for the study the patient was asked if he/she wanted to participate in the study. After providing written informed consent, the patient was enrolled in the study. If HbA1c was > 11% the patient was assessed by the study investigators, and the patient was referred to his/her physician.

Intervention

The patient was prescribed 10 units insulin glargine at bedtime, and was asked to titrate the dose by 1 unit/day to achieve a fasting plasma glucose of ≤ 5.5 mmol/L (7, 17). The intervention also included patient education regarding insulin use, dose titration and self monitoring. Patients contacted the pharmacist when they reached a fasting plasma glucose of 6 mmol/L. All patients remained on their previously prescribed oral hypoglycemic agent(s). If the combination with insulin was not approved in Canada, the oral hypoglycemic agent was discontinued (e.g., thiazolidinedione). Adjustments were made at the discretion of the treating pharmacist based on

the most recent Canadian guidelines (8). The patient's family physician received a letter from the pharmacist to inform him/her that the patient was participating in the study.

Follow-up

Patients were followed at 2, 4, 8, 14, 20, and 26 weeks to provide ongoing care, check adherence to the insulin regimen, fasting blood sugars (measured by the patient), insulin dose and titration and adverse events. HbA1c was measured at weeks 14 and 26 using the same technique used at baseline. Family physicians were kept informed of patient's progress and any medication change after each visit.

Outcomes

The primary outcome measure was the change in HbA1c from baseline to week 26. Secondary outcomes included: Proportion of patients achieving target HbA1c (defined as HbA1c ≤7.0%), changes in oral hypoglycemic agents, quality of life and patient satisfaction using Audit of Diabetes- Dependent Quality of Life (ADDQoL), Diabetes Treatment Satisfaction Questionnaire (DTSQ) and Diabetes Treatment Satisfaction (Change) Questionnaire (DTSQc), persistence on insulin glargine (% still taking insulin at the end of follow-up), number of insulin dosage adjustments per patient, number of hypoglycemic episodes.

Sample size calculation

With a sample size of 80 patients and the following assumptions: a standard deviation of 1.1 and a 2 sided alpha of 0.05 (7) we calculated 90% power to detect a mean decrease in HbA1c of

0.4%. Since this a pragmatic, practice-based trial, the sample size was inflated to 100 to account for possible losses to follow-up.

Data analysis

The level of significance was set at 0.05. All analyses were done on intention to treat basis. Missing data were imputed using a last value carried forward strategy. The mean HbA1c between baseline and 26 weeks was compared using a paired t-test. Secondary outcomes were analyzed using paired t-tests and basic frequencies. Linear regression was used to adjust for the patients' demographics and clinical characteristics.

RxING was approved by the Health Research Ethics Board of the University of Alberta and was registered on clinicaltrials.gov (NCT01335763).

Results

We screened 356 patients with type 2 diabetes; 245 were excluded because they did not meet the HbA1c inclusion criteria. Out of the 111 eligible patients, 11 were not enrolled because they refused to use insulin, leaving 100 patients enrolled (Figure 1)

The demographic and clinical characteristics of the patients are reported in Table 1. The mean age was 64 years (Standard Deviation (SD) 10.4) and had a diabetes duration of 10.2 years (SD 7). Fifty-eight percent of the patients were male, 77% were married and 90% reported having at least high school education. Nearly half of the patients (48%) were retired, almost ninety percent (89%) were white (ethnicity was self reported) and nearly half (47%) have a government medication coverage. Around one quarter of the patients (22%) reported that they were smokers, and m~~M~~ore than half (54%) reported occasional consumption of alcohol (e.g. 1-3 drinks/week). Nearly two thirds of the patients had elevated blood pressure (63%) and elevated cholesterol (64%) (hypertension and high cholesterol were self reported).

All but 1 patient was taking insulin glargine at the end of the study (he stopped his insulin before the final visit because his plasma glucose readings were "good"). At the end of the study the mean insulin glargine dose was 31.1 units (SD 18.4) with a mean of 21.1 dose adjustments (SD 18.8) per patient.

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Only 40% of the patients returned quality of life and treatment satisfaction questionnaires. Of those, only 30 ~~of those~~ questionnaires were analyzable. Quality of life and treatment satisfaction have improved by 0.2 and 1.5 respectively amongst the patients who returned the questionnaires.

~~There was an apparent slight increase in the b~~Body mass index (BMI) ~~and waist circumference between baseline and the end of the study~~ was ~~but this increase was not statistically significant~~ ~~(~~31.6 (SD 6.3) at baseline, and ~~to~~ 32.6 (SD 6.3) at the end of follow-up (~~,~~ p=0.29), and waist circumference was ~~and~~ 106 cm (SD 13.8) at baseline and ~~to~~ 107.4 cm (SD 12.9) at the end of followup (~~,~~ p=0.5 ~~respectively~~).

"Hypoglycemic-type" -symptoms were reported by 54 patients. Only 2 of these episodes required medical attention (one caused a visit to the family physician while the other required a visit to the emergency department without an overnight stay). We were not able to confirm that these episodes were true hypoglycemia, via blood glucose measurements, nor did we have baseline information on such symptoms .

Discussion

We found that a community pharmacist prescribing intervention in patients with poorly controlled type 2 diabetes improved patients' HbA1c by an absolute value of 1.8% (95% CI 1.4-2, p<0.001) and fasting plasma glucose by 4.1 mmol/L (95% CI of 3.3-5, p= 0.007). This is the first study of independent prescribing by pharmacists in patients with diabetes and represents a clinically important improvement in glycemic control.

Our findings are consistent with the findings of Gerstein and colleagues (2006) and Harris and colleagues (2008) who compared the effect of adding insulin glargine to the oral hypoglycemic regimen versus the conventional therapy where oral hypoglycemic agent doses were adjusted. They reported better glycemic control in the insulin glargine group after 26 weeks of follow up (7, 9). Our findings are also consistent with the findings of Wubben and Vivian (2008) who conducted a systematic review to assess the effectiveness of pharmacist intervention in patients with diabetes in outpatient settings. They reported additional HbA1c reduction (when compared to usual care) of 0.5% when pharmacists did not have prescribing authority and 1% when pharmacists had prescribing authority (collaborative prescribing in this case) (13).

It has been reported in the literature that the adherence rates to the insulin regimen are unsatisfactory (19); however in our study, 99% of the patients were adherent to their treatment regimen for 6 months, this can be explained by the intensive intervention provided by the pharmacist and the relatively short duration of the study.

~~The slight increase in BMI and waist circumference in our study is consistent with the findings of Heine and colleagues (2005) and Russell-Jones and colleagues (2009) who compared the efficacy of insulin glargine to an active diabetes treatment and reported that there was a slight increase in BMI and waist circumference in patients who used insulin glargine after 26 weeks (20, 21).~~

This study is not without limitations. The 26 week follow up period can be considered relatively short; it is possible that with a longer study more patients may have achieved the target HbA1c (or fewer if patients discontinued their insulin). Patients who were unwilling to use insulin were excluded from the study; however patients' willingness to use insulin was high in our pilot study (4) and also during the screening process. The proactive and systematic approach that we used in this study also helped in identifying patients who could benefit from insulin. We acknowledge that adding insulin to the oral hypoglycemic agent(s) regimen is one of the options which are available to improve glycemic control; however this choice was based on the insulin's efficacy and safety profile. The response rate to quality of life and treatment satisfaction questionnaires was low; however the improvements in quality of life and treatment satisfactions are consistent with the findings of Gerstein and colleagues (2006) who reported improvements in treatment satisfaction in the insulin glargine group (7). We also received unsolicited comments from different patients highlighting their pleasure and satisfaction with treatment and its impact on their daily activities.

We did observe a number of "hypoglycemic-~~type~~ like" symptoms", however we were not able to confirm these as true hypoglycemia. We also have no frame of reference as patients may have experienced some of these symptoms prior to enrolling in our study. Finally, the number of

reported “hypoglycemic-type symptoms” in this study was consistent with the findings of a meta analysis of more than 1100 diabetes patients who were using insulin glargine (20).

Our findings take the evidence for the benefits of pharmacist care in diabetes one step further. That prescribing insulin improves glycemic control in itself is perhaps not surprising; what is important is that pharmacists can systematically identify patients with poor glycemic control, educate and support patients to achieve better outcomes. Since pharmacists see patients with diabetes frequently (11), this can be an attractive approach.

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Role of the Sponsors: The funders had no role in the design and conduct of the study; in the collection, analysis, and interpretation of the data; or in the preparation, review, or approval of the final manuscript.

Contributors: All the authors have made substantial contributions to the manuscript. These contributions are as the following: Al Hamarneh had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design*: Tsuyuki and Charrois. *Acquisition of data*: Tsuyuki and Al Hamarneh. *Analysis and interpretation of data*: Tsuyuki and Al Hamarneh. *Drafting of the manuscript*: Tsuyuki and Al Hamarneh. *Critical revision of the manuscript for important intellectual content*: Tsuyuki, Lewanczuk, Charrois and Al Hamarneh. *Statistical analysis*: Tsuyuki and Al Hamarneh. *Administrative, technical, and material support*: Tsuyuki, Lewanczuk, Charrois and Al Hamarneh. *Study supervision*: Tsuyuki and Lewanczuk.

Competing interests: None declared

Ethics approval: Health Research Ethics Board of the University of Alberta

Data sharing statement: All obtained data have been analysed and reported in the manuscript. Any further queries can be resolved by contacting the authors

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Table 1 Demographic and clinical characteristics of the patients (N=100)

Characteristic	Frequency
Gender	
Male	58
Female	42
Marital status	
Single	8
Married	77
Divorced	9
Widowed	6
Education	
Grade School	10
High School	36
Some post secondary education	26
Post secondary education	28
Employment	
Caring for family	1
Working for profit/pay	36
Unemployed/looking for a job	6
Retired	48
Other	9

Self reported Ethnicity	
Aboriginal/first nation	1
White	89
South Asian	1
Oriental	4
Other	4
Declined	1
Medication coverage	
Private	29
Government	47
Out of pocket	15
Private and government	7
Private and out of pocket	2
Smoking status	
Smoker	22
Ex-smoker	41
Non-smoker	37
Alcohol consumption	
No Alcohol	43
Occasional alcohol (e.g. 1-3 drinks/week)	54
1-2 alcohol drinks per day	3

Self reported Hypertension	
Yes	63
No	36
Unknown	1
Self reported high cholesterol	
Yes	64
No	33
Unknown	3

Table 2 Number of oral hypoglycemic agents used by patients and Mean HbA1c

Number of oral agents	Frequency	Mean HbA1c (SD)
1	34	8.7 (0.9)
2	56	9.1 (0.9)
3	7	9.8 (1.6)
4	3	8.7 (0.7)

Table 3 Oral hypoglycemic use at baseline and the end of the study

Medication	Baseline (N=100)	26 weeks (N=93)
Metformin	88	78
Sulfonylurea	54	32
Meglitinides	18	29
DPP4	12	3
Thiazolidinedione	9	0

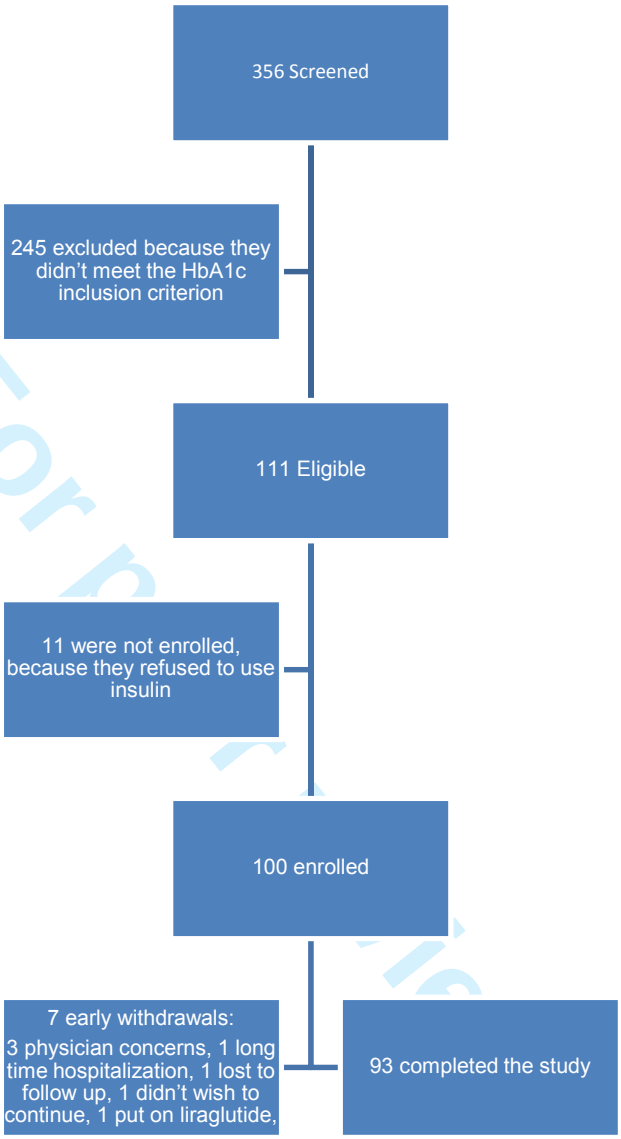

Figure 1 Patients' screening and enrollment flow chart

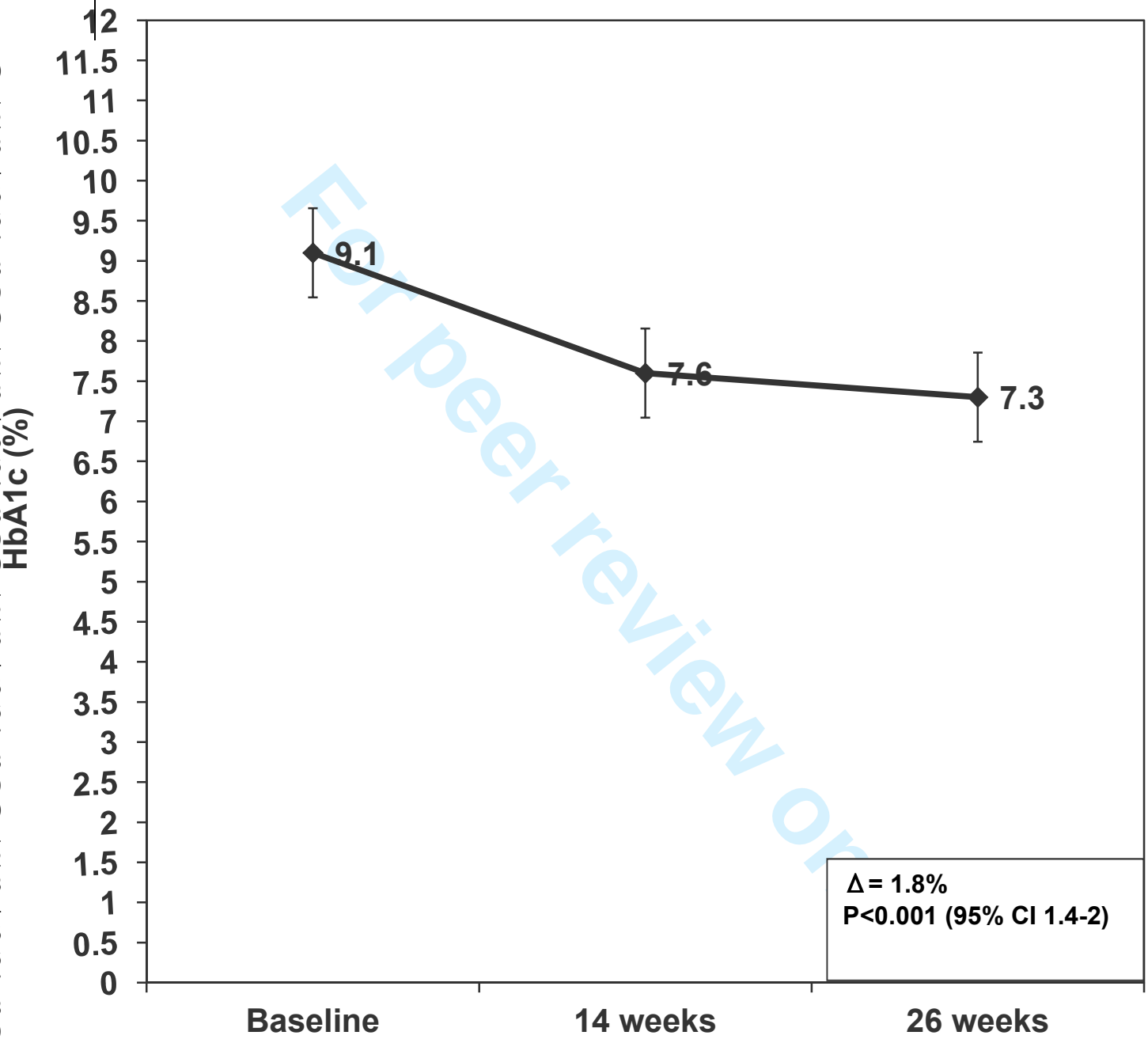

Figure 2 Intervention effect on HbA1c in patients with uncontrolled type 2 diabetes (n=100)

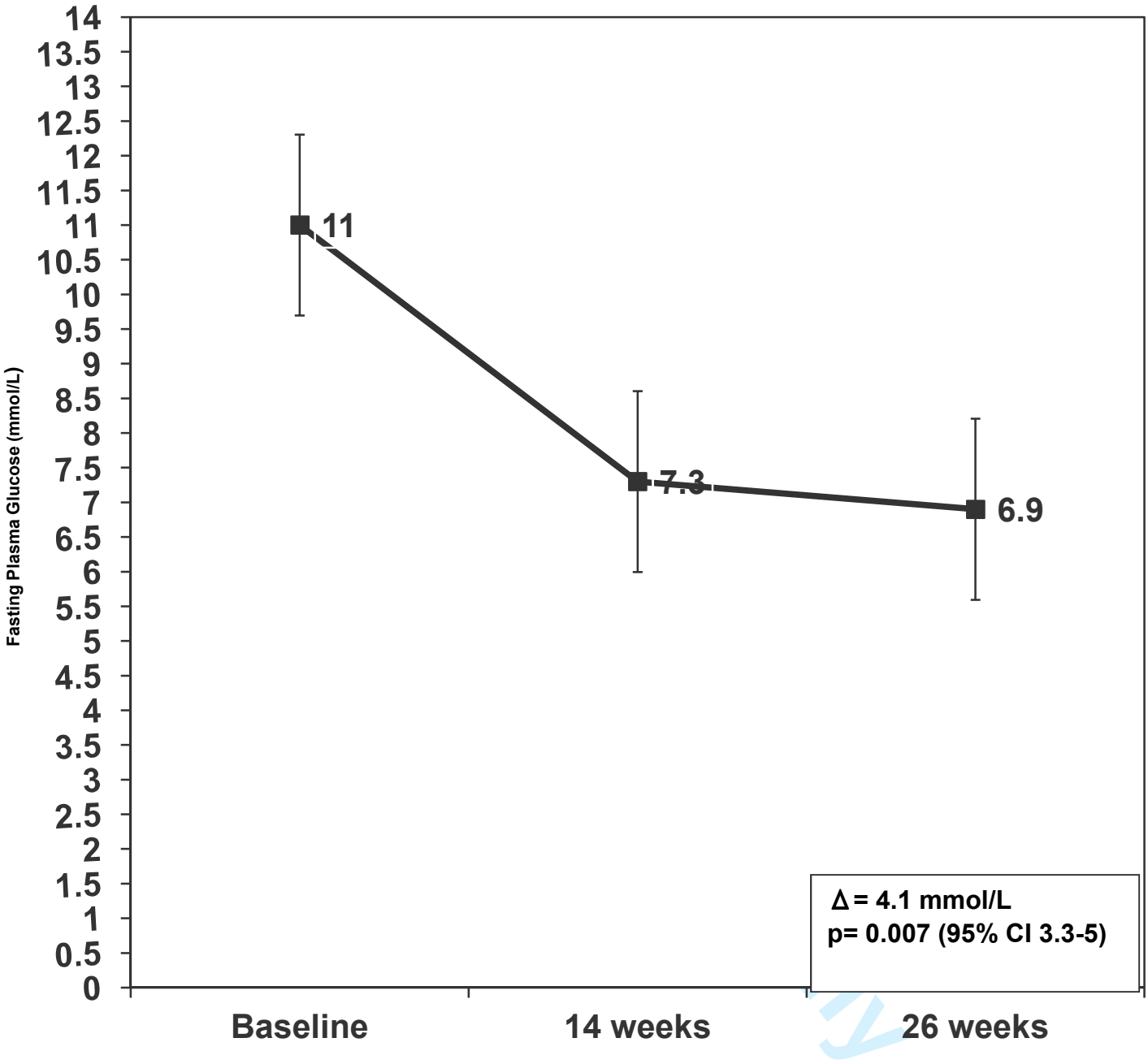

Figure 3 Intervention effect on fasting plasma glucose in patients with uncontrolled type 2 diabetes (n=100)

Pharmacist Intervention for Glycemic Control in the Community (The RxING study)

Yazid N Al Hamarneh, PhD, EPICORE Centre, Division of Cardiology, Department of Medicine, University of Alberta

Theresa Charrois, MSc, School of Pharmacy, Curtin University

Richard Lewanczuk, MD, PhD, Department of Medicine, University of Alberta

Ross T Tsuyuki, PharmD, MSc, Professor of Medicine and Director, EPICORE Centre, Division of Cardiology, Department of Medicine, University of Alberta (Corresponding author)

EPICORE Centre

220 College Plaza

University of Alberta

Edmonton, Alberta

T6G 2C8

Tel: 780-492-8526

Fax: 780-492-6059

ross.tsuyuki@ualberta.ca

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Figures: 3

Abstract

Objective: To determine the effect of a community pharmacist prescribing intervention on glycemic control in patients with poorly controlled type 2 diabetes.

Design: Pragmatic, before-after design

Setting: 12 community pharmacies in Alberta, Canada.

Participants: Type 2 diabetes receiving oral hypoglycemic medications and with HbA1c of 7.5-11%

Intervention: Pharmacists systematically identified potential candidates by inviting patients with Type 2 diabetes to test their HbA1c using validated point of care technology ~~(DCA Vantage®)~~. Pharmacists prescribed 10 units of insulin glargine at bedtime, adjusted by increments of 1 unit daily to achieve a morning fasting glucose of ≤5.5mmol/L. The patients were followed at 2, 4, 8, 14, 20, and 26 weeks.

Primary outcome: Change in HbA1c from baseline to week 26.

Secondary outcomes: Proportion of patients achieving target HbA1c, changes in oral hypoglycemic agents, quality of life and patient satisfaction, persistence on insulin glargine, number of insulin dosage adjustments per patient and number of hypoglycemic episodes.

Results: We screened 365 patients of whom 111 were eligible. Of those, 100 (90%) were enrolled in the study; all 11 patients who did not consent refused to use insulin. Average age was 64 years (~~standard deviation (~~SD~~)~~ 10.4), while average diabetes duration was 10.2 years (SD 7). HbA1c was reduced from 9.1% (SD 1) at baseline to 7.3% (SD 0.9) a change of 1.8% (95% CI 1.4-2, p<0.001). Fasting plasma glucose was reduced from 11 mmol/l (SD 3.3) to 6.9 mmol/l (SD 1.8), a change of 4.1 mmol/l (95% CI of 3.3-5, p= 0.007). Fifty one percent of the patients achieved the target HbA1c of ≤ 7% at the end of the study.

Conclusion: This is the first completed study of independent prescribing by pharmacists. Our results showed similar improvements in glycemic control as previous physician-led studies. RxING provides further evidence for the benefit of pharmacist care in diabetes.

Trial registration: clinicaltrials.gov; Identifier: NCT01335763

Article summary

Article focus:

To determine the effect of a community pharmacist prescribing intervention on glycemic control in patients with poorly controlled type 2 diabetes.

Key Messages:

- Community pharmacist prescribing intervention on glycemic control in patients with poorly controlled type 2 diabetes reduced patients' HbA1c from 9.1% at baseline to 7.3% at 26 weeks, a change of 1.8%. While fasting plasma glucose (FPG) was reduced from 11 mmol/L at baseline to 6.9 mmol/L at 26 weeks, a change of 4.1 mmol/L
- Pharmacists can systematically identify patients with poor glycemic control, educate and support them to achieve better outcomes
- Since pharmacists see patients with diabetes frequently, we recommend getting the pharmacists more involved in delivering the care for patients with type 2 diabetes

Strengths and limitations of the study:

- This is the first study of independent prescribing by pharmacists in patients with diabetes and it demonstrates a clinically important improvement in glycemic control.
- The 26 week follow up period can be considered relatively short; it is possible that with a longer study more patients may have achieved the target HbA1c (or fewer if patients discontinued their insulin).
- We did observe a number of "hypoglycemic-type symptoms", however we were not able to confirm these as true hypoglycemia. We also have no frame of reference as patients may have experienced some of these symptoms prior to enrolling in our study. Finally,

the number of reported “hypoglycemic-type symptoms” in this study was consistent with the findings reported in the literature.

Financial acknowledgements: This work was supported by unrestricted investigator-initiated funding provided by Sanofi Canada and the testing equipments were provided by ManthaMed.

Role of the Sponsors: The funders had no role in the design and conduct of the study; in the collection, analysis, and interpretation of the data; or in the preparation, review, or approval of the manuscript.

Introduction

Currently, 347 million individuals are living with diabetes worldwide (1). Approximately 90% of those individuals have type 2 diabetes (1). The number of new cases of type 2 diabetes is rapidly increasing mainly because of obesity and an ageing population (2).

Because of its chronic nature and the severe complications associated with it, diabetes carries a health and a financial burden on the affected individual and health systems (3). Poorly controlled diabetes puts patients at high risk of suffering from macrovascular and microvascular complications (4).

Type 2 diabetes is a progressive disease; it has been reported that 50% of the insulin producing capacity is lost at the time of diagnosis with an average loss rate of 5% per year afterwards (5). As a result, many patients with type 2 diabetes will eventually require the use of insulin; however, clinicians seem reluctant to start insulin (6) despite the evidence from studies such as INSIGHT, which demonstrated improved glycemic control with the addition of insulin glargine to oral hypoglycemic agents in patients with type 2 diabetes (7) as well as guidelines that recommending starting insulin immediately if the patients HbA1c is ≥ 9% (8).

Clinicians' reluctance to initiating insulin due to unfamiliarity with the treatment or using it as a last resort (9) plays a major role in influencing the patient's decision to commence insulin treatment regimen. It has been reported that many patients have 'psychological insulin resistance' where they are unwilling to take insulin because of certain beliefs that insulin will not

be beneficial and in some cases it may even be harmful. Personal experience and messages from different healthcare professionals can also affect the patient's decisions regarding insulin treatment regimen (6, 10).

Pharmacists are front line healthcare professionals who see patients with diabetes more frequently than physicians (15 times/year Vs 7 times/year) (11) and as such, could proactively and systematically identify patients with poorly controlled type 2 diabetes in a broad-based public health approach to chronic disease management (12). Indeed, there is good evidence for the efficacy of pharmacist care in diabetes (13). In community settings, pharmacists have demonstrated that they are capable of identifying poorly controlled patients, educate patients regarding diabetes, medications and self-monitoring of plasma glucose, provide adherence support, identify and resolve diabetes problems and complications and setting goals in order reduce the patients' HbA1c, plasma glucose and improve their quality of life and other co-morbidities (4, 12 - 16). Moreover, the scope of practice for pharmacists in Alberta is changing, allowing pharmacists to prescribe medications and order laboratory tests. As such, there is an unprecedented opportunity to identify and improve glycemic control in patients with type 2 diabetes.

The main aim of the RxING study was to determine the effect of a community pharmacist prescribing intervention on glycemic control in patients with poorly controlled type 2 diabetes.

Methods

Study design and setting

RxING was a multicentre pragmatic before-after design trial, which was conducted in 12 community pharmacies in the province of Alberta, Canada.

We chose the before-after design because we had concerns about withholding insulin from this high risk group. Those concerns were based on guidelines recommendations (8) and the evidence from studies such as INSIGHT (7).

All participating pharmacists, who were either certified diabetes educators (CDE) or preparing to be CDE, received face to face training by the study team. The training material was based on the most recent Canadian guidelines and recommendations (7,8). They also received a manual of operations to help them conduct the study.

Study participants

We recruited adults -who had physician diagnosed type 2 diabetes for at least six months and were receiving one or more oral hypoglycemic agents, had a HbA1c between 7.5% and 11%, and who were willing to sign an informed consent.

We excluded patients who were unwilling to use insulin, previously or currently using insulin (confirmed by the patient's medication records), had a history of ketoacidosis (confirmed by the patient's healthcare records), were pregnant, worked night shifts, had renal impairment (serum creatinine of ≥ 124 mmol/l for females or ≥ 133 mmol/l for males) (confirmed by the patient's

healthcare records), ~~,~~ were clinically unstable (based on the pharmacist's judgment), were unwilling or unable to attend follow-up visits, or felt to be unlikely to adhere to study procedures due to cognitive limitations (based on the pharmacist's judgment), severe psychiatric disorders or alcoholism (confirmed by the patient's healthcare records).

Recruitment

Pharmacists systematically identified potential candidates from within their practice by inviting patients with type 2 diabetes (e.g., patients on metformin) to test their HbA1c in the pharmacy using validated point of care technology (DCA Vantage®, Siemens, Tarrytown, New York, USA). If the result of the HbA1c test was high (7.5-11 %) and the patient met the other inclusion criteria for the study the patient was asked if he/she wanted to participate in the study. After providing written informed consent, the patient was enrolled in the study. If HbA1c was > 11% the patient was assessed by the study investigators, and the patient was referred to his/her physician.

Intervention

The patient was prescribed 10 units insulin glargine at bedtime, and was asked to titrate the dose by 1 unit/day to achieve a fasting plasma glucose of ≤ 5.5 mmol/L (7, 17). The intervention also included patient education regarding insulin use, dose titration and self monitoring. Patients contacted the pharmacist when they reached a fasting plasma glucose of 6 mmol/L. All patients remained on their previously prescribed oral hypoglycemic agent(s). If the combination with insulin was not approved in Canada, the oral hypoglycemic agent was discontinued (e.g., thiazolidinedione). Adjustments were made at the discretion of the treating pharmacist based on

the most recent Canadian guidelines (8). The patient's family physician received a letter from the pharmacist to inform him/her that the patient was participating in the study.

Follow-up

Patients were followed at 2, 4, 8, 14, 20, and 26 weeks to provide ongoing care, check adherence to the insulin regimen, fasting blood sugars (measured by the patient), insulin dose and titration and adverse events. HbA1c was measured at weeks 14 and 26 using the same technique used at baseline. Family physicians were kept informed of patient's progress and any medication change after each visit.

Outcomes

The primary outcome measure was the change in HbA1c from baseline to week 26. Secondary outcomes included: Proportion of patients achieving target HbA1c (defined as HbA1c ≤7.0%), changes in oral hypoglycemic agents, quality of life and patient satisfaction using Audit of Diabetes- Dependent Quality of Life (ADDQoL), Diabetes Treatment Satisfaction Questionnaire (DTSQ) and Diabetes Treatment Satisfaction (Change) Questionnaire (DTSQc), persistence on insulin glargine (% still taking insulin at the end of follow-up), number of insulin dosage adjustments per patient, number of hypoglycemic episodes.

Sample size calculation

With a sample size of 80 patients and the following assumptions: a standard deviation of 1.1 and a 2 sided alpha of 0.05 (7) we calculated 90% power to detect a mean decrease in HbA1c of

0.4%. Since this a pragmatic, practice-based trial, the sample size was inflated to 100 to account for possible losses to follow-up.

Data analysis

The level of significance was set at 0.05. All analyses were done on intention to treat basis. Missing data were imputed using a last value carried forward strategy. The mean HbA1c between baseline and 26 weeks was compared using a paired t-test. Secondary outcomes were analyzed using paired t-tests and basic frequencies. Linear regression was used to adjust for the patients' demographics and clinical characteristics.

RxING was approved by the Health Research Ethics Board of the University of Alberta and was registered on clinicaltrials.gov (NCT01335763).

Results

We screened 356 patients with type 2 diabetes; 245 were excluded because they did not meet the HbA1c inclusion criteria. Out of the 111 eligible patients, 11 were not enrolled because they refused to use insulin, leaving 100 patients enrolled (Figure 1)

The demographic and clinical characteristics of the patients are reported in Table 1. The mean age was 64 years (Standard Deviation (SD) 10.4) and had a diabetes duration of 10.2 years (SD 7). Fifty-eight percent of the patients were male, 77% were married and 90% reported having at least high school education. Nearly half of the patients (48%) were retired, almost ninety percent (89%) were white (ethnicity was self reported) and nearly half (47%) have a government medication coverage. Around one quarter of the patients (22%) reported that they were smokers, and m~~M~~ore than half (54%) reported occasional consumption of alcohol (e.g. 1-3 drinks/week). Nearly two thirds of the patients had elevated blood pressure (63%) and elevated cholesterol (64%) (hypertension and high cholesterol were self reported).

All but 1 patient was taking insulin glargine at the end of the study (he stopped his insulin before the final visit because his plasma glucose readings were "good"). At the end of the study the mean insulin glargine dose was 31.1 units (SD 18.4) with a mean of 21.1 dose adjustments (SD 18.8) per patient.

HbA1c was reduced from 9.1% (SD 1) at baseline to 7.3% (SD 0.9) at 26 weeks, a change of 1.8% (95% CI 1.4-2, $p<0.001$) (Figure 2). While fasting plasma glucose (FPG) was reduced from

11 mmol/L (SD 3.3) at baseline to 6.9 mmol/L (SD 1.8) at 26 weeks, a change of 4.1 mmol/L (95% CI of 3.3-5, p= 0.007) (Figure 3).

Fifty one percent of the patients achieved the target HbA1c of ≤ 7% at the end of the study. At baseline, two thirds (66%) of the patients were taking two or more medications (Table 2), the most widely used combination was metformin and gliclazide, followed metformin and glyburide and metformin and repaglinide. Nearly half of the patients (48%) had their oral hypoglycemic regimen altered (Table 3); the most frequent alterations were stopping sulfonylurea (46%) followed by initiating meglitinides (23%), stopping metformin (21%) and stopping thiazolidinedoine and DPP4 inhibitors (19%). Those alterations were made by the pharmacists who then informed the patients' family physicians.

Only 40% of the patients returned quality of life and treatment satisfaction questionnaires. Of those, only 30 ~~of those~~ questionnaires were analyzable. Quality of life and treatment satisfaction have improved by 0.2 and 1.5 respectively amongst the patients who returned the questionnaires.

~~There was an apparent slight increase in the b~~Body mass index (BMI) ~~and waist circumference between baseline and the end of the study~~ was ~~but this increase was not statistically significant~~ (~~31.6 (SD 6.3)~~ at baseline, and ~~to~~ 32.6 (SD 6.3) at the end of follow-up (~~,~~ p=0.29), and waist circumference was ~~and~~ 106 cm (SD 13.8) at baseline and ~~to~~ 107.4 cm (SD 12.9) at the end of followup (~~,~~ p=0.5 ~~respectively~~).

"Hypoglycemic-type" -symptoms were reported by 54 patients. Only 2 of these episodes required medical attention (one caused a visit to the family physician while the other required a visit to the emergency department without an overnight stay). We were not able to confirm that these episodes were true hypoglycemia, via blood glucose measurements, nor did we have baseline information on such symptoms .

Discussion

We found that a community pharmacist prescribing intervention in patients with poorly controlled type 2 diabetes improved patients' HbA1c by an absolute value of 1.8% (95% CI 1.4-2, p<0.001) and fasting plasma glucose by 4.1 mmol/L (95% CI of 3.3-5, p= 0.007). This is the first study of independent prescribing by pharmacists in patients with diabetes and represents a clinically important improvement in glycemic control.

Our findings are consistent with the findings of Gerstein and colleagues (2006) and Harris and colleagues (2008) who compared the effect of adding insulin glargine to the oral hypoglycemic regimen versus the conventional therapy where oral hypoglycemic agent doses were adjusted. They reported better glycemic control in the insulin glargine group after 26 weeks of follow up (7, 9). Our findings are also consistent with the findings of Wubben and Vivian (2008) who conducted a systematic review to assess the effectiveness of pharmacist intervention in patients with diabetes in outpatient settings. They reported additional HbA1c reduction (when compared to usual care) of 0.5% when pharmacists did not have prescribing authority and 1% when pharmacists had prescribing authority (collaborative prescribing in this case) (13).

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~~The slight increase in BMI and waist circumference in our study is consistent with the findings of Heine and colleagues (2005) and Russell-Jones and colleagues (2009) who compared the efficacy of insulin glargine to an active diabetes treatment and reported that there was a slight increase in BMI and waist circumference in patients who used insulin glargine after 26 weeks (20, 21).~~

This study is not without limitations. The 26 week follow up period can be considered relatively short; it is possible that with a longer study more patients may have achieved the target HbA1c (or fewer if patients discontinued their insulin). Patients who were unwilling to use insulin were excluded from the study; however patients' willingness to use insulin was high in our pilot study (4) and also during the screening process. The proactive and systematic approach that we used in this study also helped in identifying patients who could benefit from insulin. We acknowledge that adding insulin to the oral hypoglycemic agent(s) regimen is one of the options which are available to improve glycemic control; however this choice was based on the insulin's efficacy and safety profile. The response rate to quality of life and treatment satisfaction questionnaires was low; however the improvements in quality of life and treatment satisfactions are consistent with the findings of Gerstein and colleagues (2006) who reported improvements in treatment satisfaction in the insulin glargine group (7). We also received unsolicited comments from different patients highlighting their pleasure and satisfaction with treatment and its impact on their daily activities.

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reported “hypoglycemic-type symptoms” in this study was consistent with the findings of a meta analysis of more than 1100 diabetes patients who were using insulin glargine (20).

Our findings take the evidence for the benefits of pharmacist care in diabetes one step further. That prescribing insulin improves glycemic control in itself is perhaps not surprising; what is important is that pharmacists can systematically identify patients with poor glycemic control, educate and support patients to achieve better outcomes. Since pharmacists see patients with diabetes frequently (11), this can be an attractive approach.

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Table 1 Demographic and clinical characteristics of the patients (N=100)

Characteristic	Frequency
Gender	
Male	58
Female	42
Marital status	
Single	8
Married	77
Divorced	9
Widowed	6
Education	
Grade School	10
High School	36
Some post secondary education	26
Post secondary education	28
Employment	
Caring for family	1
Working for profit/pay	36
Unemployed/looking for a job	6
Retired	48
Other	9

Self reported Ethnicity	
Aboriginal/first nation	1
White	89
South Asian	1
Oriental	4
Other	4
Declined	1
Medication coverage	
Private	29
Government	47
Out of pocket	15
Private and government	7
Private and out of pocket	2
Smoking status	
Smoker	22
Ex-smoker	41
Non-smoker	37
Alcohol consumption	
No Alcohol	43
Occasional alcohol (e.g. 1-3 drinks/week)	54
1-2 alcohol drinks per day	3

Self reported Hypertension	
Yes	63
No	36
Unknown	1
Self reported high cholesterol	
Yes	64
No	33
Unknown	3

Table 2 Number of oral hypoglycemic agents used by patients and Mean HbA1c

Number of oral agents	Frequency	Mean HbA1c (SD)
1	34	8.7 (0.9)
2	56	9.1 (0.9)
3	7	9.8 (1.6)
4	3	8.7 (0.7)

Table 3 Oral hypoglycemic use at baseline and the end of the study

Medication	Baseline (N=100)	26 weeks (N=93)
Metformin	88	78
Sulfonylurea	54	32
Meglitinides	18	29
DPP4	12	3
Thiazolidinedione	9	0

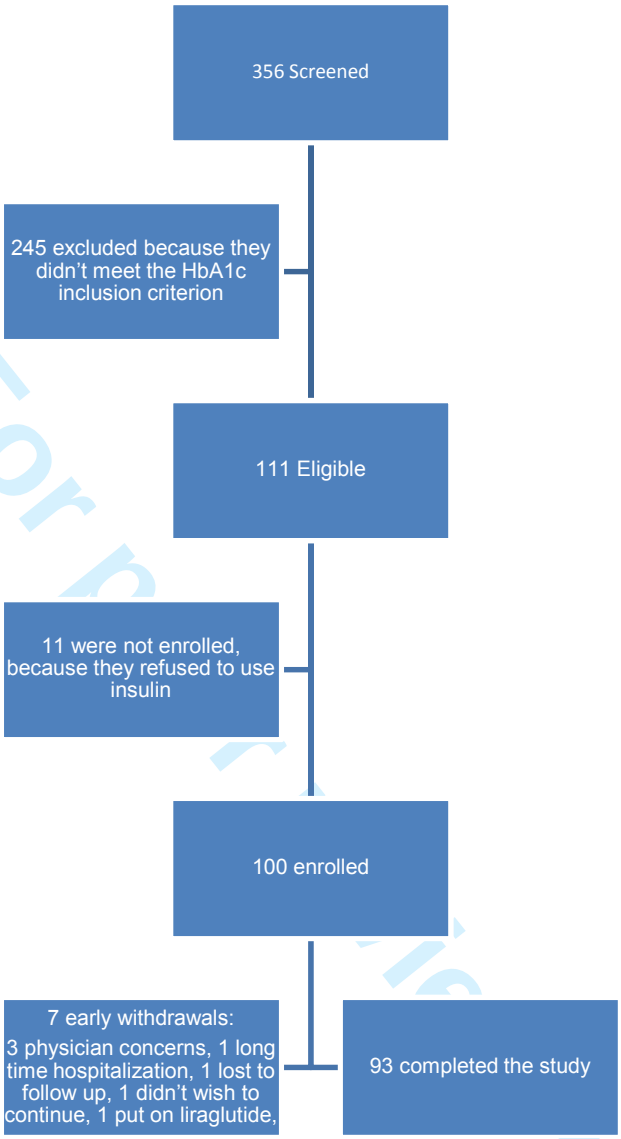

Figure 1 Patients' screening and enrollment flow chart

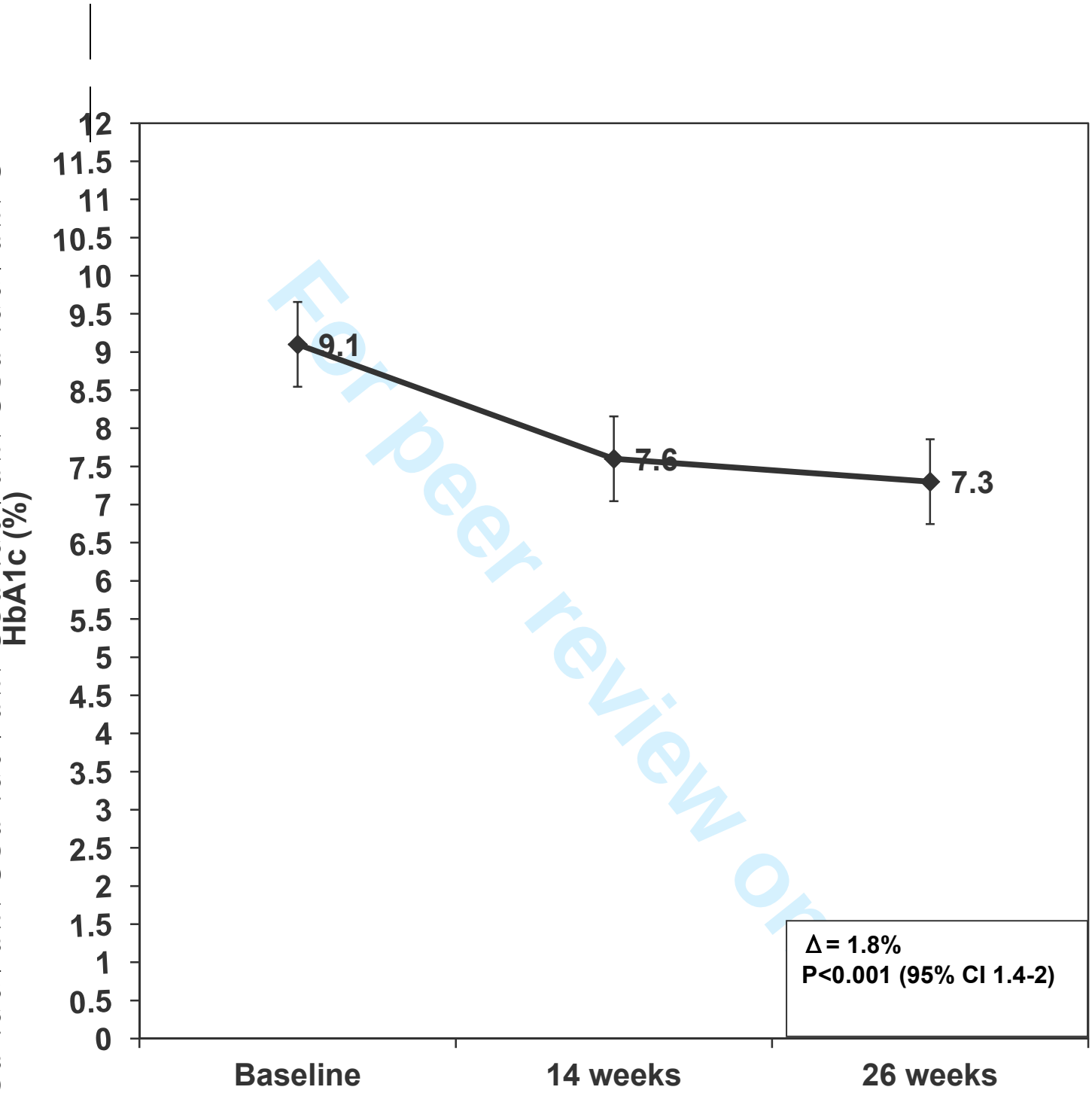

Figure 2 Intervention effect on HbA1c in patients with uncontrolled type 2 diabetes (n=100)

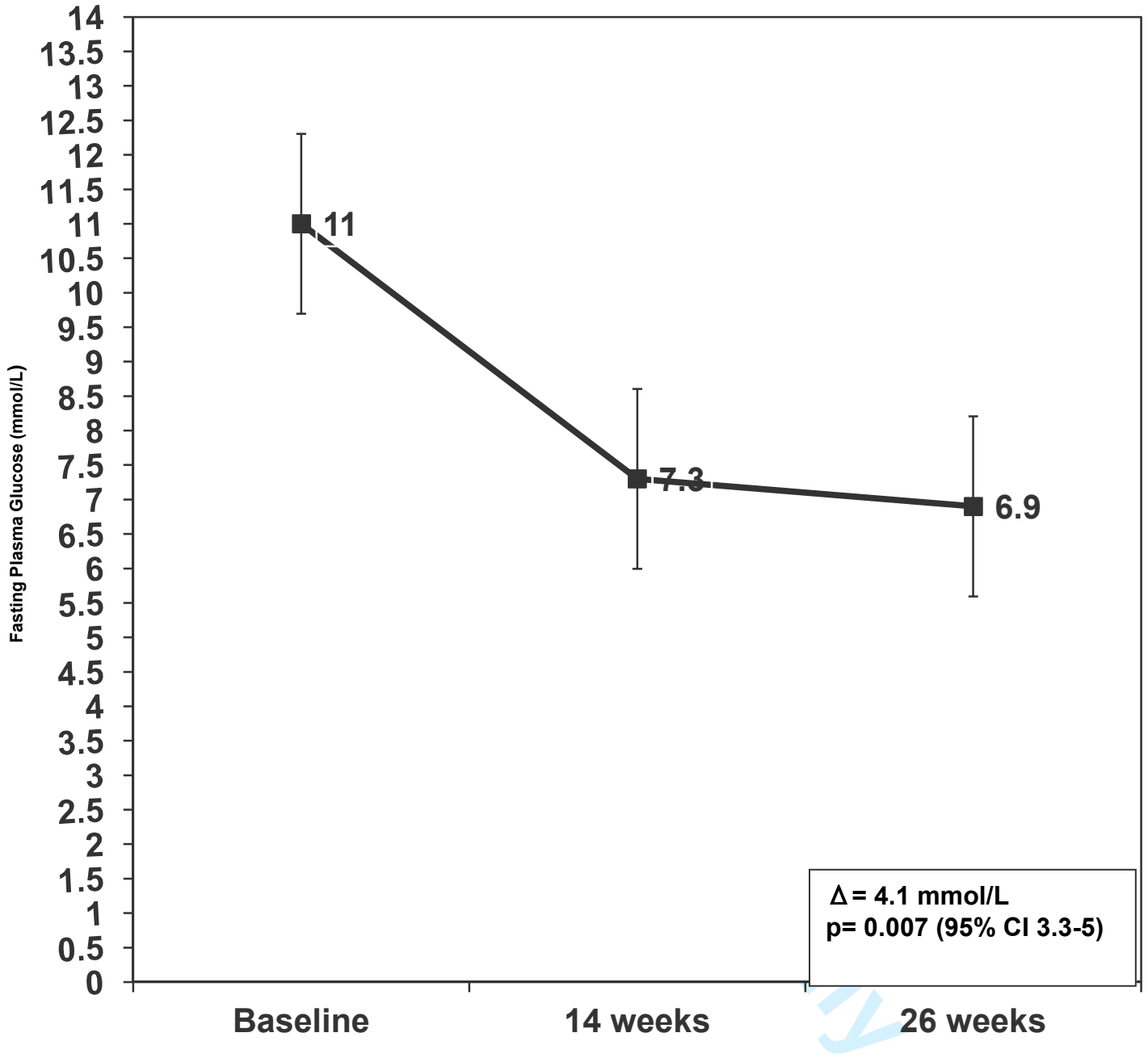

Figure 3 Intervention effect on fasting plasma glucose in patients with uncontrolled type 2 diabetes (n=100)