Intensification of Insulin Therapy in Family Practice – Keeping It Simple

Stewart B. Harris MD MPH FCFP FACPM
Professor, Family Medicine
Canadian Diabetes Association Chair in Diabetes Management
Ian McWhinney Chair of Family Medicine Studies
Schulich School of Medicine & Dentistry
Western University
London, Ontario, Canada

Funding and Disclosures

- This study was sponsored by Sanofi Canada.
- S.B. Harris made the following declarations:
  - Consulting and advisory board honoraria from Sanofi, Lilly, Novo Nordisk, Janssen, Merck, Takeda, Boehringer Ingelheim, Bristol-Myers Squibb, and AstraZeneca
  - Lecture honoraria from Sanofi, Novo Nordisk, Lilly, Astra Zeneca, and Merck
  - Funds given to his institution for research or educational initiatives by Sanofi, Merck, and Novo Nordisk

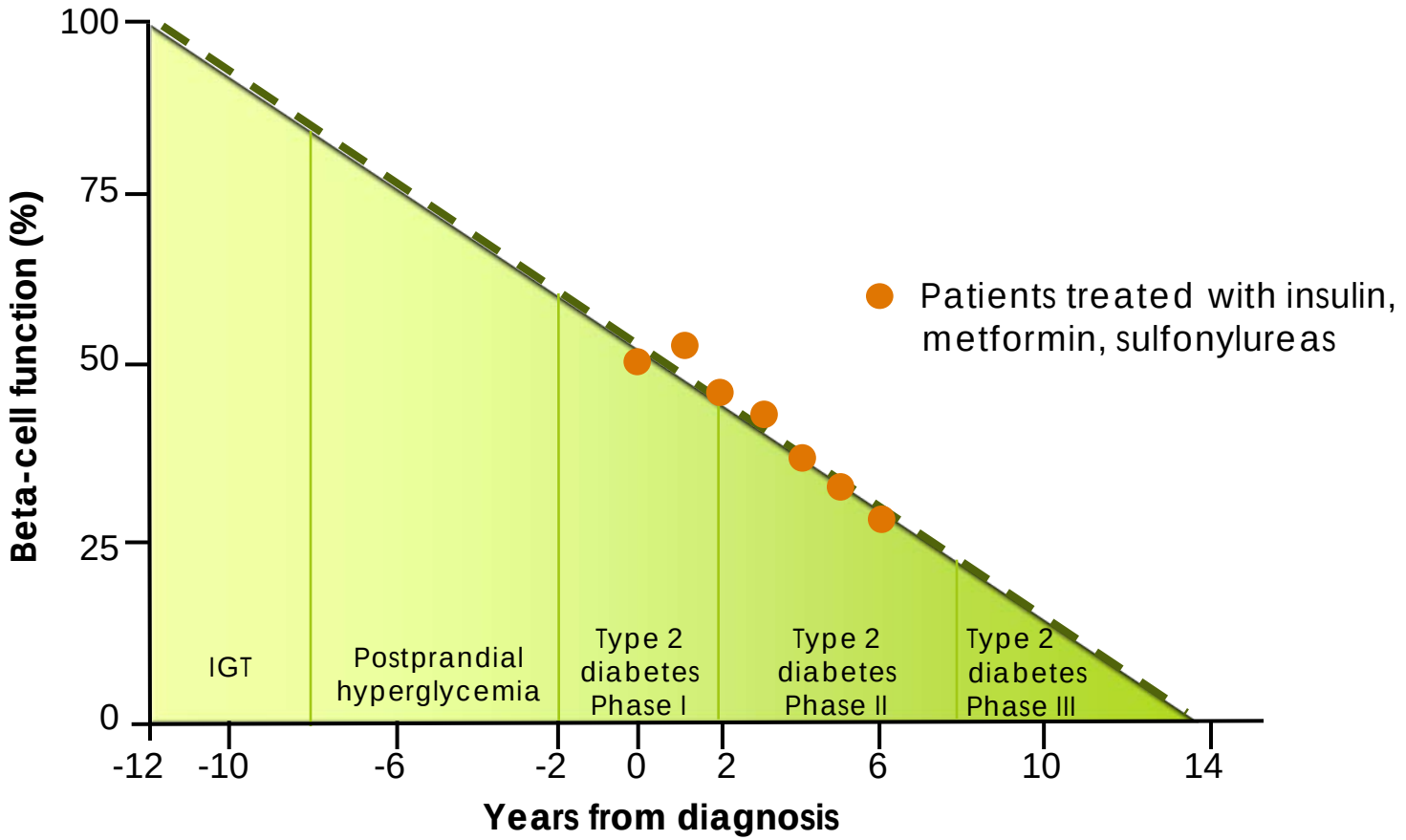
Clinical trial registration #: NCT01013571

Objectives

- To understand clinical inertia around insulin therapy in family practice
- To review results of a basal plus strategy (START trial)

Clinical Inertia in the Treatment of Type 2 Diabetes in Canada

Type 2 Diabetes is a Progressive Disease

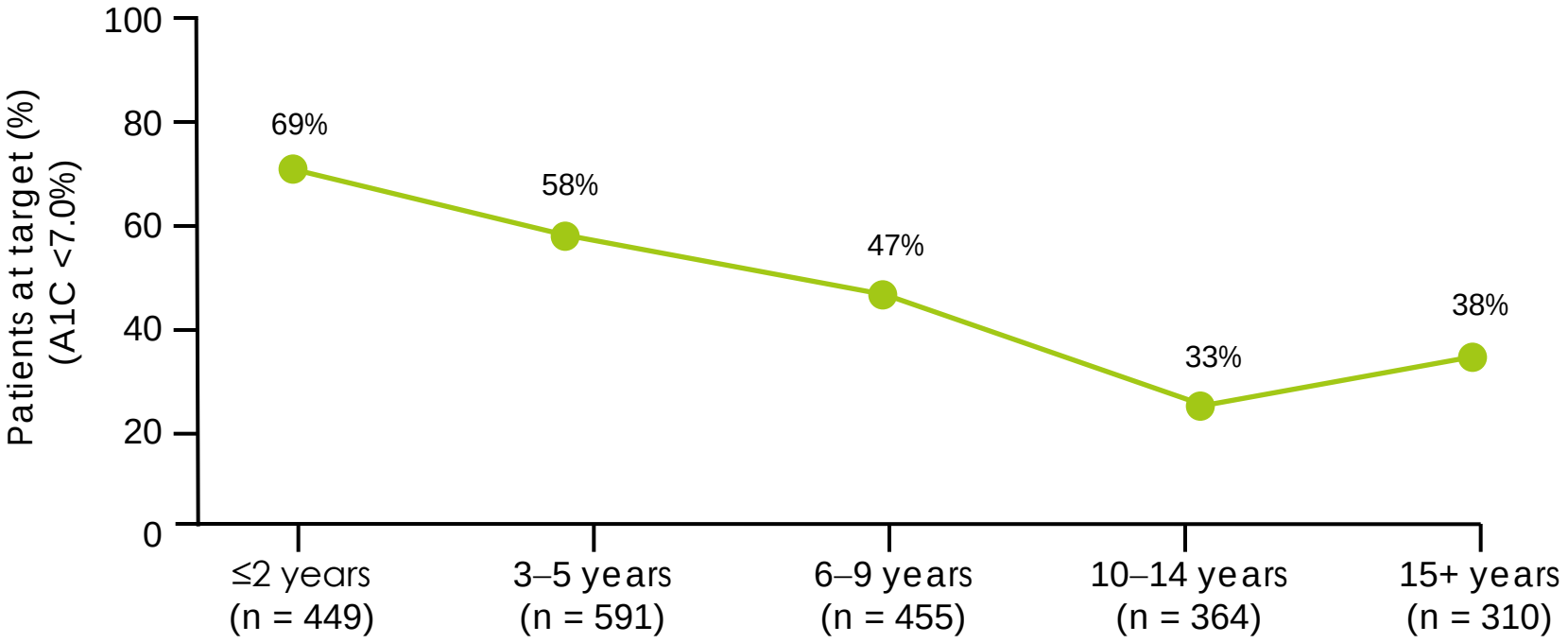


UKPDS = United Kingdom Prospective Diabetes Study

Lebovitz HE. *Diabetes Rev.* 1999;7:139-53.

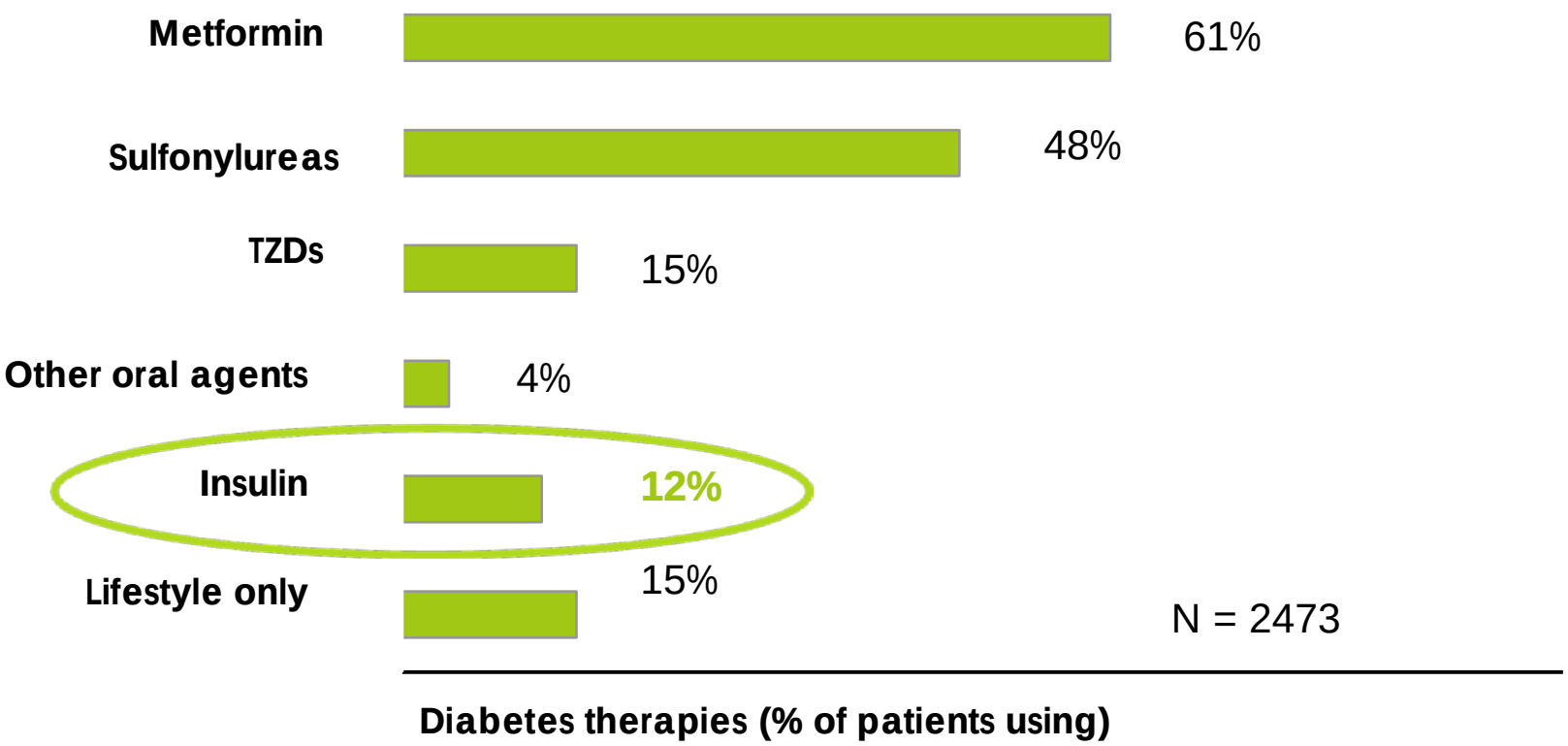
Control Erodes the Longer Patients Have Type 2 Diabetes

- Only 38% of patients who have had diabetes for 15+ years are well controlled.



Harris SB, et al. *Diabetes Res Clin Pract*. 2005:70:90-97.

Underutilization of Insulin Therapy: 2005



Harris SB, et al. *Diabetes Res Clin Pract*. 2005;70:90-97.

Underutilization of Insulin Therapy: 2011

- In a Canadian cohort of 2335 participants with type 2 diabetes and:
  - Mean age of 62.9 years
  - Mean duration of diabetes of 10.6 years
  - High prevalence of complications/comorbidities
- **20% reported using insulin**

1. Baillot A, et al. *Diabetes Res Clin Pract*. 2014:103:11-19.

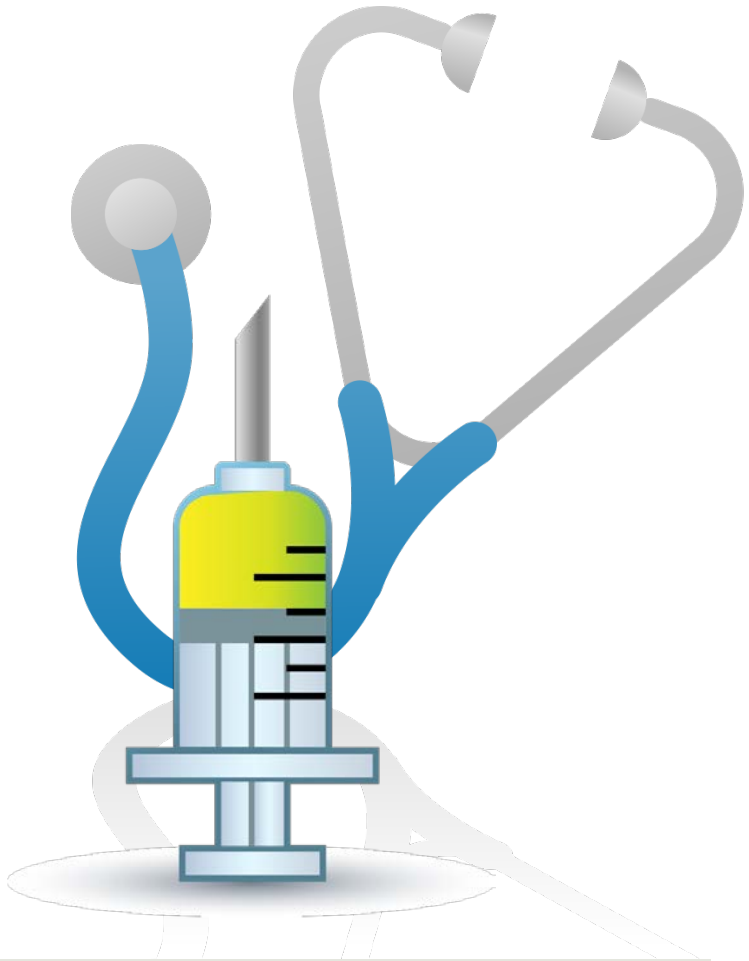
Insulin Therapy – Too Late and Too Little

- Mean time to insulin initiation: **9.2 years**
- Mean A1C values were:
  - **9.5%** before insulin initiation
  - **8.1%** at visit 2 (median 1.2 years later), and
  - **7.9%** at visit 3 (median 3.9 years after initiation).
- At visit 3, 20% of patients continued to have very poor glycemic control (A1C >9.0%).

Harris SB, et al. *Can Fam Phys*. 2010;56:418-24.

Insulin Intensification Must Happen in the Primary Care Setting

- **Family physicians** must accept the responsibility of intensifying insulin therapy
- It is **currently poorly done** – insulin initiation happens too late and is not aggressive enough
- There is a **need for simplified approaches** that are effective, safe and feasible.



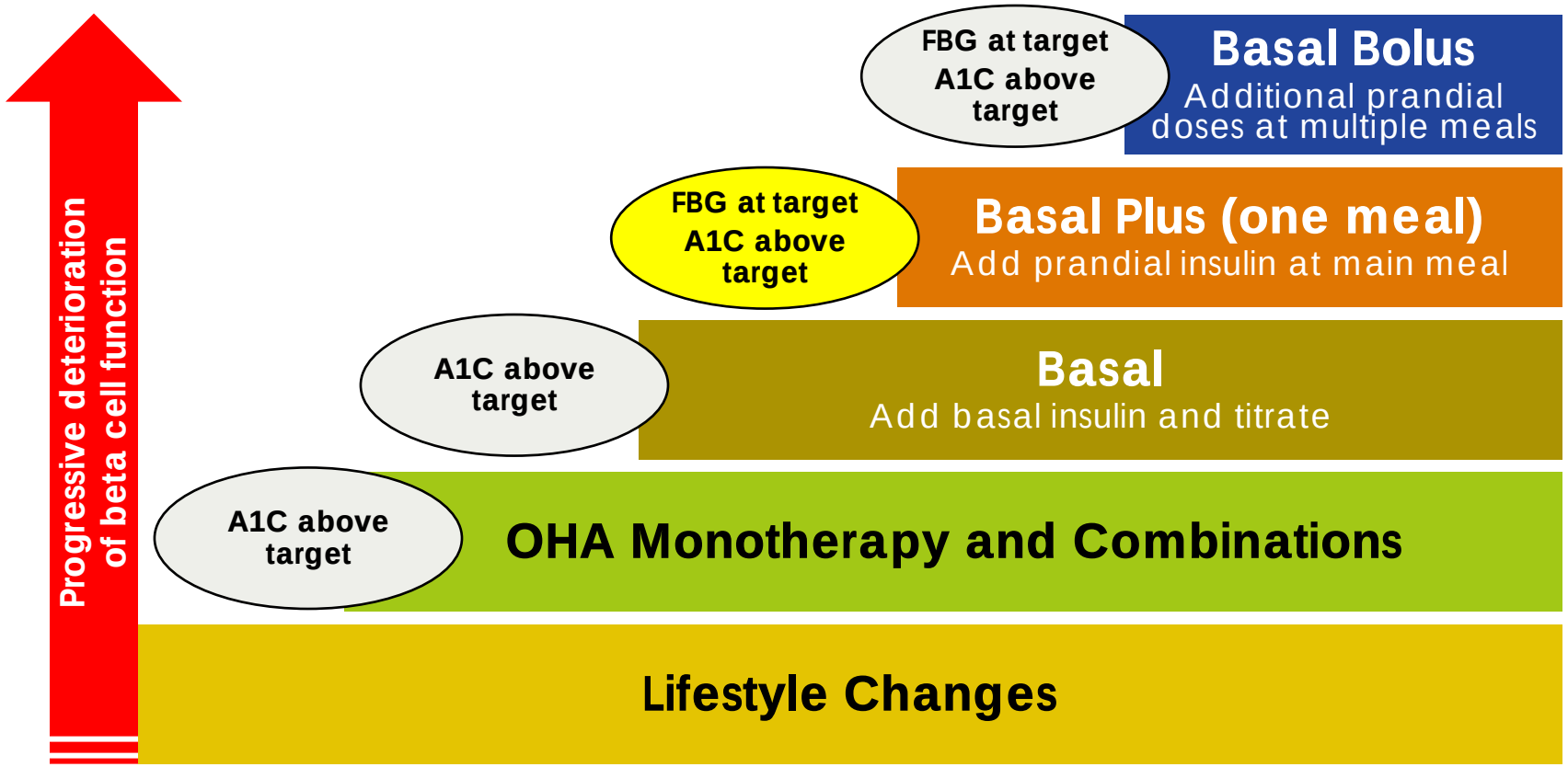
Harris SB, et al. *Diabetes Care*. 2014;37:604-10.

Stepwise Approaches to Treatment Intensification

A Progressive Disease Requires Progressive Treatment

- Basal insulin analogs are often added to oral anti-hyperglycemic agents (OADs)
- Over time, basal insulin may not be sufficient to maintain optimal control
- The following indicate need for addition of prandial (bolus) insulin:
  - A1C levels remain above target, despite acceptable fasting values with basal insulin (indicating increased postprandial values)
  - Inability to further uptitrate basal insulin due to nocturnal hypoglycemia

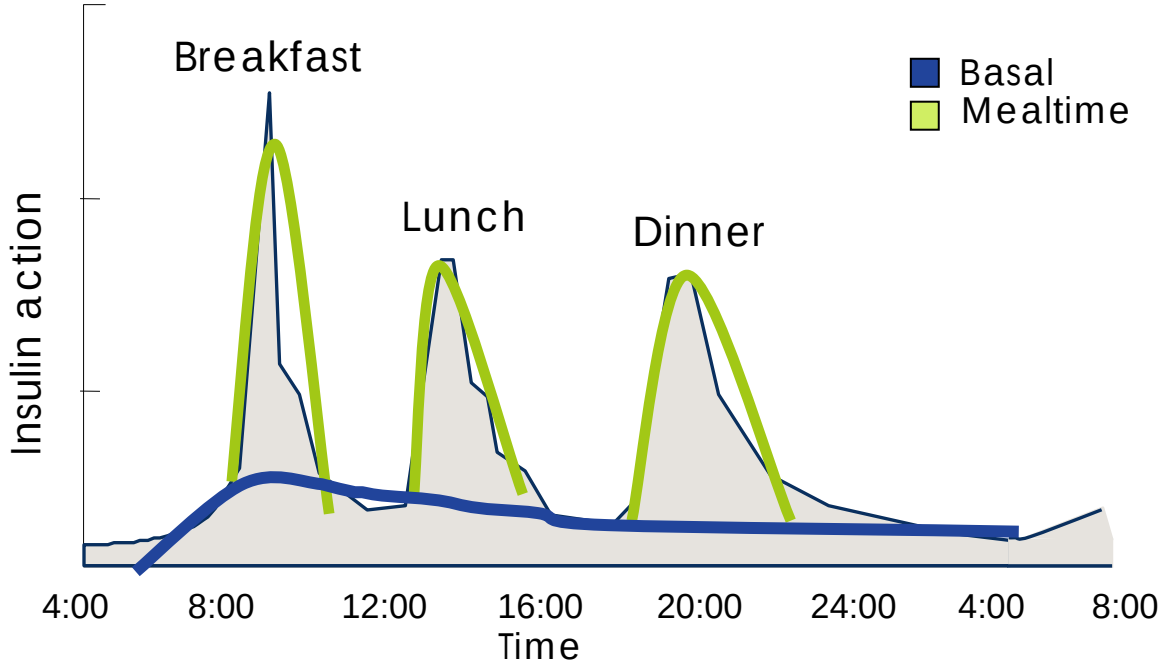
Keeping It Simple – A Stepwise Approach to Therapy



OHA = oral hypoglycemic agent

Adapted from Raccah D, et al. *Diabetes Met Res Rev*. 2007;23(4):257-64.

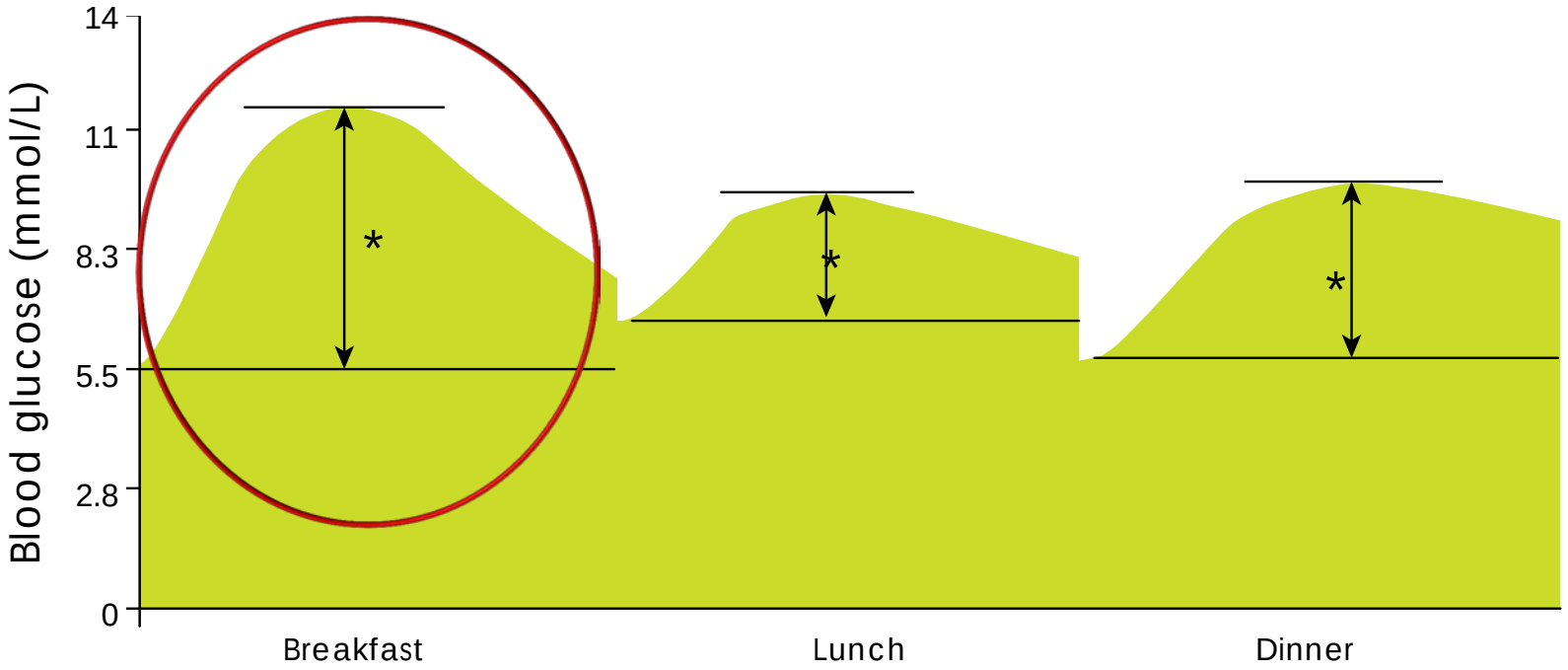
Analogue Insulins More Closely Match Physiologic Insulin Profile



- ✓ A long-acting insulin analogue (detemir, glargine) may be considered as an alternative to an intermediate-acting as the basal insulin.
- ✓ Rapid-acting insulin analogues should be considered over regular insulin.

2013 CDA Clinical Practice Guidelines. *Can J Diabetes*. 2013;37(suppl 1):S1-S212.

Breakfast is the Largest Glycemic Excursion of the Day



- For the same carbohydrate intake, the peak blood glucose excursion was two times greater at breakfast and was two-thirds greater at dinner than lunch.[1]
- When patients with type 2 diabetes evenly consume carbohydrate throughout the day (70 g per meal), they display a higher blood glucose excursion at breakfast than at lunch or dinner.[2]
- This may be due to the "dawn phenomenon."

*peak blood glucose excursion

1. Figure adapted from: Franc S, et al. *Diabetes Care*. 2010;33:1913–18.
2. Pearce KL, et al. *Am J Clin Nutr.* 2008;87:638–44.

Rationale for the START Study

- As family physicians care for the vast majority of patients with type 2 diabetes, they **must** learn how to intensify insulin.
- Family physicians frequently cite their own fear of inducing hypoglycemia and time constraints as barriers to intensifying insulin.[1]
- Increasing acceptance of strategies that progressively add bolus to basal insulin. However… the best way to do this is unclear.
- Could a patient-driven algorithm for bolus insulin work as it has for basal insulin?
- **START**: Could a patient-driven self-titration algorithm achieve glycemic control that was comparable to that achieved by physician-titrated bolus insulin?

1. Harris SB, et al. ADA 68th Scientific Sessions, San Francisco, CA, June 6-10, 2008. Abstract 455-P.

Does a Patient-Managed Insulin Intensification Strategy With Insulin Glargine and Insulin Glulisine Provide Similar Glycemic Control as a Physician-Managed Strategy? Results of the START (Self-Titration With Apidra to Reach Target) Study

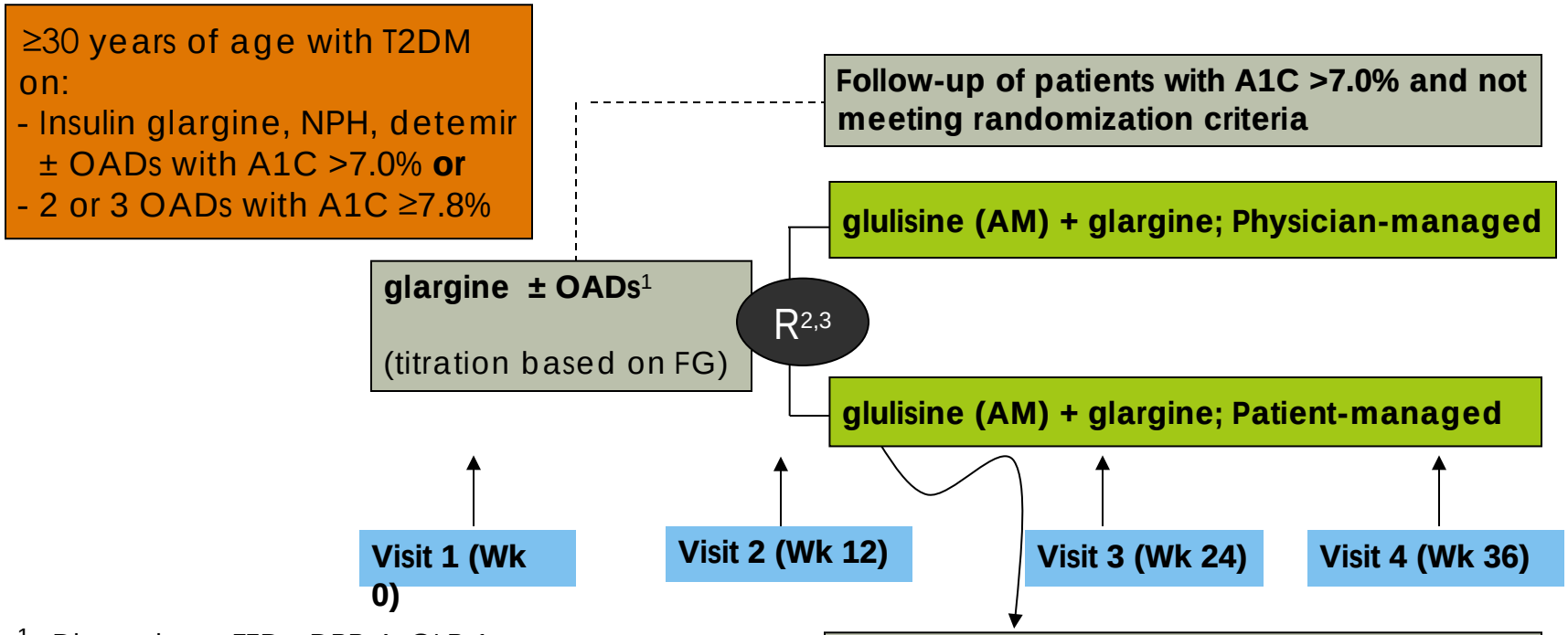
A Randomized Noninferiority Trial

Stewart B. Harris,[1] Jean-François Yale,[2] Lori Berard,[3] John Stewart,[4] Babak Abbaszadeh,[4] Susan Webster-Bogaert,[1] and Hertzel C. Gerstein[5]

OBJECTIVE

Diabetes self-management is universally regarded as a foundation of diabetes care. We determined whether comparable glycemic control could be achieved by self-titration versus physician titration of a once-daily bolus insulin dose in patients with type 2 diabetes who are unable to achieve optimal glycemia control with a basal insulin.

START Study Design



1 Discontinue: TZDs, DPP-4, GLP-1

2 If A1C >7.0%; and ≥1 episode of confirmed nocturnal hypoglycemia **or** FG ≤6.0 mmol/L (based on at least 2 BG values in previous week)

3 Discontinue SU if daytime hypoglycemia occurs

Harris SB, et al. *Diabetes Care*. 2014;37:604–10.

Run-In Phase Protocol

- Patients were switched from their previous basal insulin therapy to once-daily insulin glargine in the evening,
  - Initiation dose at switch
    - Same dose for NPH once daily 20% reduction of total dose of NPH twice daily
    - 30% reduction of insulin detemir
  - Dose titration
    - Increased by 1 IU/day, to obtain FPG levels of ≤5.5 mmol/L
- OADs remained the same (TZD and DPP-IV discontinued)
- Starting dose of insulin glargine for insulin- naïve patients: 10 IU

Harris SB, et al. *Diabetes Care*. 2014;37:604–10.

Intervention – All Patients

- After randomization, all patients:
  - Continued receiving their fixed glargine dose, and
  - Added insulin glulisine before breakfast.
  - Were instructed to eat their usual breakfast
  - Were not required to log their diet.

Harris SB, et al. *Diabetes Care*. 2014;37:604–10.

Rationale For Adding Glulisine at Breakfast

- To **maximize patient safety** by reducing the risk of nocturnal hypoglycemia
- To expand on **common practice**. Many patients receiving a basal insulin routinely test their blood glucose in the morning. The addition of a breakfast prandial insulin self-titration algorithm requires **only one extra self-monitoring** test later in the same morning.
- Patient **convenience** of injecting at home
- Optimization of blood glucose levels earlier in the day may help to maintain good glycemic control for the **remainder of the day**; and
- It may be easier for patients to pursue self-titration for injection at subsequent meals in their future care.

Harris SB, et al. *Diabetes Care*. 2014;37:604–10.

Primary Outcome Measure

- Achievement of an **A1C level of ≤7% without severe hypoglycemia** 24 weeks after randomization.
  - Severe hypoglycemia defined as:
    - Required assistance and FPG level <2.0 mmol/L or responded to counteractive treatment
- Test of non-inferiority was performed
  - If the lower end of the CI was **-5.0% or greater**, the patient-managed arm was deemed non-inferior to the physician-managed arm.

Harris SB, et al. *Diabetes Care*. 2014;37:604–10.

START Study - Results

Patient Characteristics

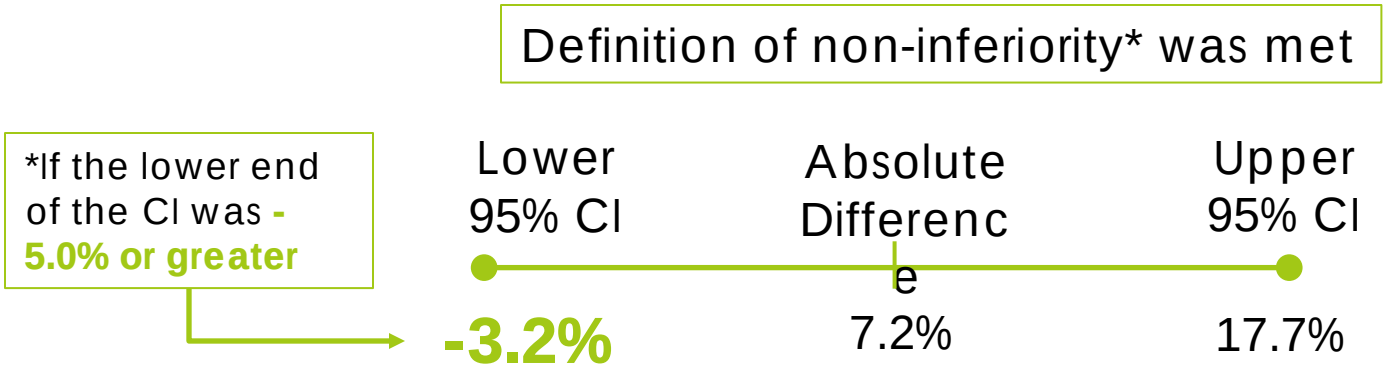
Patient Characteristics*	Patient-managed Group (N = 154)	Physician-managed Group (N = 162)	P value
Age, years, mean (SD)	60.4 (10.0)	60.2 (9.8)	0.72
Duration of diabetes, years, mean (SD)	12.1 (8.0)	12.2 (8.6)	0.86
A1C, %, mean (SD)	8.2 (0.8)	8.3 (1.3)	0.86
BMI, kg/m^2, mean (SD)	34.1 (7.2)	34.3 (7.9)	0.74
Patients with diabetes-related complications at screening, n (%)	47 (30.5)	57 (35.2)	0.38

* At randomization

Harris SB, et al. *Diabetes Care*. 2014;37:604–10.

Primary Outcome

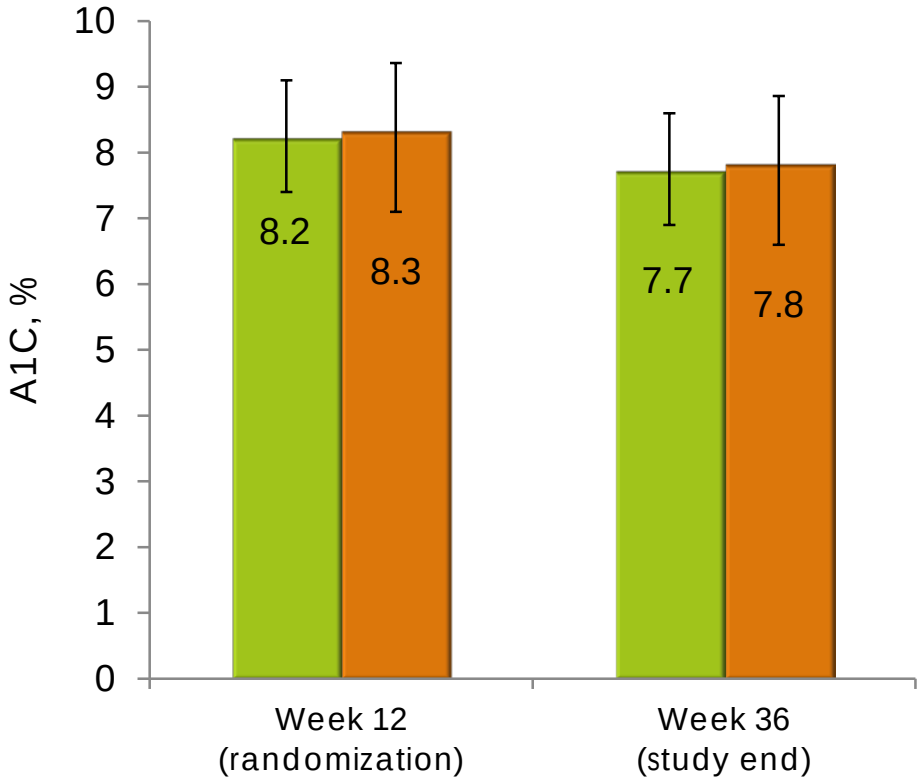
- Double primary outcome: Achievement of an **A1C level of ≤7% without severe hypoglycemia**
- After a mean follow-up time of 159.4 days (SD 36.2), the primary outcome was achieved by:
  - **28.4% of subjects in the patient-managed arm**
  - **21.2% in the physician-managed arm**



Harris SB, et al. *Diabetes Care*. 2014;37:604–10.

Secondary Outcome – A1C

- **A1C decreased** significantly for **both** groups.
- No statistically significant differences **between** groups.



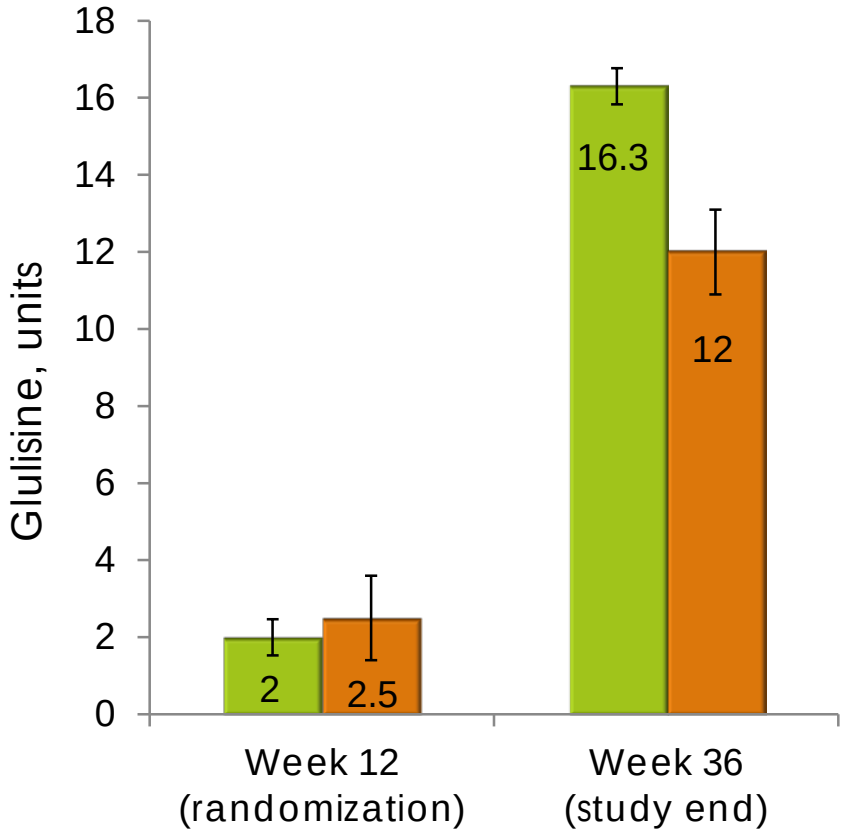
- Within-group p values 0.0001 (for both)
- Between-group p value 0.49

Patient-managed

Physician-managed

Harris SB, et al. *Diabetes Care*. 2014;37:604–10.

Secondary Outcome – Glulisine Dose



- This increase was significantly **higher** by the end of treatment for **patient**-managed group
- Adjusted mean difference of 5.6 units (SE 1.77) (95% CI 2.1–9.1, P = 0.0018)

Patient-managed

Physician-managed

Harris SB, et al. *Diabetes Care*. 2014;37:604–10.

Secondary Outcome – Hypoglycemia

Patients with at least one symptomatic hypoglycemic episode

	Patient-managed group (N = 154)	Physician-managed group (N = 162)	95% CI	P value
Any hypoglycemic episode	67.5%	61.1%	-17.0 to 4.1	0.23
- Annualized episode rate*	13.2	13.0	0.76 to 1.28	0.93
Any confirmed episode	63.6%	58.6%	-15.7 to 5.7	0.36
- Annualized episode rate*	11.1	10.4	0.71 to 1.28	0.65
Any episode <3.1 mmol/L	33.8%	30.9%	-13.2 to 7.4	0.58
- Annualized episode rate*	2.9	2.3	0.52 to 1.26	0.34
Any nocturnal episode	26.0%	28.4%	-7.4 to 12.2	0.63
- Annualized episode rate*	3.5	2.9	0.58 to 1.15	0.25
Any severe episode	1.9%	1.9%	-3.1 to 2.9	0.95
- Annualized episode rate*	1.3	1.7	0.32 to 5.62	0.69

Majority of hypoglycemic events occurred between 6:00 AM and noon, patient-managed 58.3%, physician-managed 62.7%.

* N per person per year

Harris SB, et al. *Diabetes Care*. 2014;37:604–10.

Secondary Outcome – Hypoglycemia

Annualized episode rates*, entire patient population

	Patient-managed group (N = 154)	Physician-managed group (N = 162)	95% CI	P value
Hypoglycemic episodes	8.9	8.1	0.62 to 1.32	0.61
Confirmed episodes	7.1	6.2	0.60 to 1.29	0.51
Episodes <3.1 mmol/L	1.4	3.6	0.45 to 1.25	0.27
Nocturnal episodes	0.9	0.8	0.53 to 1.58	0.75
Severe episodes	0.02	0.03	0.24 to 9.32	0.68

* N per person per year

Harris SB, et al. *Diabetes Care*. 2014;37:604–10.

Secondary Outcomes – Hypoglycemia, Weight, Rx Satisfaction

Hypoglycemia

- No difference between the groups for the proportion of patients who experienced a minimum of one hypoglycemic event.
- The majority of hypoglycemic events occurred between 6:00 AM and noon.

Weight

- Mean body weight **significantly increased for both** groups
- Between-group analysis showed a significantly higher increase for the patient-managed group. Adjusted mean difference of 0.87 kg

Satisfaction

- Patients ranked their mean **satisfaction as "high"** by the end of their treatment
- By the end of the trial, the majority of physicians reported a very **high level of confidence** initiating and intensifying insulin therapy.

Harris SB, et al. *Diabetes Care*. 2014;37:604–10.

START Study Conclusions – What Did We Learn in This Real-World Trial?

- A **patient-driven algorithm for bolus insulin works** in the primary care setting (non-inferior to physician-managed)
- Using a titration approach at **breakfast** works
- The **patients** who were responsible for managing their insulin titration **were more aggressive at titrating glulisine** when compared with the physician-managed group

Harris SB, et al. *Diabetes Care*. 2014;37:604–10.

Many Patients in Primary Care Require Prandial (Bolus) Insulin

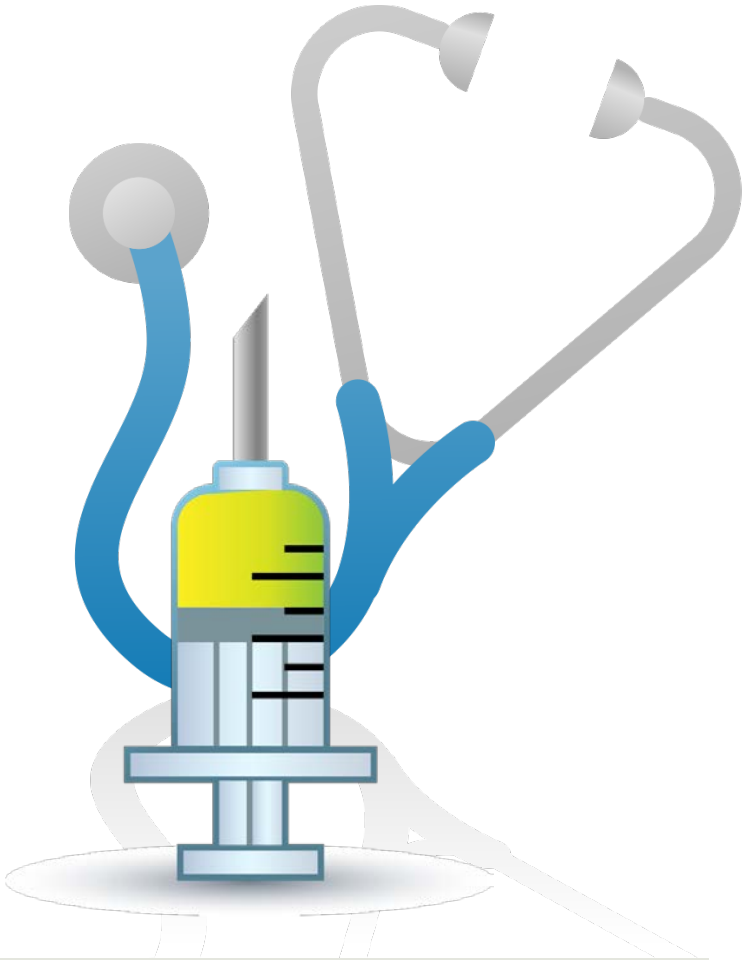
- **INSIGHT trial: 50% of patients** were not on target, even after optimization of basal insulin.[1]

- **START study: 56% of patients** to whom basal insulin was prescribed **required prandial insulin** intensification after the 12-week run-in phase.[2]

1. Gerstein HC, et al. *Diabet Med*. 2006;23:736–42.
2. Harris SB, et al. *Diabetes Care*. 2014;37:604–10.

Insulin Intensification is a Dynamic Process

- Only **21% and 28%** of patients in this trial achieved optimal control **with** no severe hypoglycemia
- Highlights the **need for ongoing intensification**
  - i.e. additional bolus therapy at other meals may be required



Harris SB, et al. *Diabetes Care*. 2014;37:604–10.

Summary and Conclusions

- The START study demonstrated that a simple basal plus **patient-driven treatment algorithm was as safe and effective as a physician-driven algorithm**.
- This builds on the **feasibility** of using patient-driven algorithms **in the primary care setting**.
- A **simple safe** way to intensify insulin therapy when basal insulin alone fails.
- A useful strategy for family physicians who treat the vast majority of patients with type 2 diabetes.
- The START study offers a potential strategy to mitigate clinical inertia involving insulin intensification in the primary care setting

Harris SB, et al. *Diabetes Care*. 2014;37:604–10.