# Drug Class Review

# Newer Drugs for the Treatment of Diabetes Mellitus

**Final Report**

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# Inclusion criteria and outcomes

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- Population
  - Adults and children with type 1 and type 2 diabetes mellitus
- Health outcomes
  - All-cause mortality, micro- or macrovascular disease, quality of life including treatment satisfaction
- Intermediate outcomes
  - Glycemic control (A1c,fasting plasma glucose, post-prandial plasma glucose), change in weight, time to treatment failure
- Harms-related outcomes
  - Overall adverse events, major adverse events, and withdrawals due to adverse events
- Study design
  - Good systematic reviews, controlled clinical trials, comparative cohort studies; all ≥ 12 weeks in duration

# Literature search

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- Medline through January 2008
- Cochrane Central Registry of Controlled Trials
- Cochrane Database of Systematic Reviews
- FDA and NCCHTA web sites
  - FDA Medical and Statistical Reviews
- Pharmaceutical industry dossiers
- Hand searching of reference lists

# Overview: Pramlintide, exenatide, and sitagliptin

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- Evidence base
  - Pramlintide
    - 6 trials, 4 pooled analyses, 2 observational studies
  - Exenatide
    - 7 trials, 2 systematic reviews, 6 cohort studies
  - Sitagliptin
    - 11 trials, 2 systematic reviews
- For all 3 drugs:
  - No data on children were available
  - No studies evaluated long-term health outcomes or harms
  - No studies were longer than 52 weeks in duration

# Pramlintide

# Pramlintide:
# Key questions 1 and 3

DRUG EFFECTIVENESS REVIEW PROJECT

1. For children and adults with **type 1 diabetes** does pramlintide differ in efficacy, effectiveness, or harms in achieving glycemic control when added to insulin compared with conventional insulin therapy?

3. Are there subgroups of patients for which pramlintide is more or less suitable than other hypoglycemic agents?

# Results

DRUG EFFECTIVENESS REVIEW PROJECT

- Addition of pramlintide to *flexible-dose* insulin
  - Pramlintide 30 µg or 60 µg (before meals) plus flexible dose insulin was as effective or slightly better than placebo in reducing A1c and weight (2 trials)
  - Percent change in total daily insulin dose was larger for those on pramlintide combination compared with placebo but clinical significance is unclear (2 trials)
  - About 25% on pramlintide combination achieved A1c <7% compared with 11% on placebo at “any time” during 52 weeks (1 trial)

# Intermediate outcomes: *Flexible-dose* insulin

DRUG EFFECTIVENESS REVIEW PROJECT

| | A1c | | Weight | | Total daily insulin dose | |
|---|---|---|---|---|---|---|
| | **Pramlintide 30-60 µg[a]** | **Placebo** | **Pramlintide 30-60 µg[a]** | **Placebo** | **Pramlintide 30-60 µg[a]** | **Placebo** |
| Edelman, 2006[b] | -0.5% | -0.5% | **-1.3 kg*** | +1.2 kg | -12% | +1% |
| Whitehouse, 2002[c] | **-0.39%**** | -0.12% | -0.5 kg | +1.0 kg | **+2.3%***** | +10.3% |

[a] Administered before meals (three to four times daily).
[b] Followed prespecified glycemic goals during the trial; 29 weeks duration.
[c] Did not provide specific information regarding insulin dose adjustments; reported that insulin dose. adjustments were made according to "good medical practices"; 52 weeks duration.
*$P<0.001$ compared with placebo
**$P=0.0071$ compared with placebo
***$P=0.018$ compared with placebo

# Results


- Addition of pramlintide to *fixed- or stable-dose* insulin
  - Pramlintide 60 µg (before meals) plus fixed-dose insulin was more effective than placebo in reducing A1c and weight (1 trial)
  - Percent change in total daily insulin dose was larger for patients on pramlintide combination than placebo but clinical significance is unlikely (1 trial)
  - About 13% on pramlintide combination achieved A1c <7% compared with 4% on placebo at “any time” (1 trial)

# Intermediate outcomes: *Fixed- or stable-dose* insulin

DRUG EFFECTIVENESS REVIEW PROJECT

| | Ratner, 2004[a] | | |
|---|---|---|---|
| | **Pramlintide 60 µg TID** | **Pramlintide 60 µg QID** | **Placebo** |
| A1c | **-0.29%**[b] | **-0.34%**[c] | -0.04% |
| Weight | **-0.4 kg**[d] | **-0.4 kg**[e] | +0.8 kg |
| Total daily insulin dose | -3% | -6% | 0% |

Abbreviations: TID, three times a day; QID, four times a day.

[a] After this trial was initiated, results from a different trial indicated that 90 µg dose had an adverse tolerability profile. The 90 µg TID treatment group was prospectively excluded; 52 weeks duration.

[b] *P*=0.01 compared with placebo

[c] *P*=0.001 compared with placebo

[d] *P*=0.03 compared with placebo

[e] *P*=0.04 compared with placebo

# Withdrawals and harms

DRUG EFFECTIVENESS REVIEW PROJECT

- Total withdrawal and withdrawal due to adverse events
  - More pramlintide plus insulin > than placebo plus insulin
- No significant cardiac, hepatic, renal, or drug-related idiosyncratic adverse events were observed in any treatment group
- None of the included studies reported deaths
- Only 1 trial reported sinusitis: 14.0% with pramlintide and 8.8% with placebo but this was not statistically significant ($P>0.05$)

# Harms

DRUG EFFECTIVENESS REVIEW PROJECT

- Hypoglycemia
  - None of the trials reported general incidence of mild to moderate hypoglycemia
  - Severe hypoglycemia was reported as “event rate”
    - Weeks 0-4:
      - More pramlintide plus insulin > than placebo plus insulin
    - Weeks 0-29 and 26-52:
      - Rate ↓ as pramlintide dose was stabilized, but overall, rate remained slightly elevated compared with placebo plus insulin
    - 1 trial allowed 30%-50% reduction in prandial insulin before starting pramlintide:
      - Rates ↓ but overall rates for pramlintide plus insulin slightly > placebo plus insulin

# Harms

DRUG EFFECTIVENESS REVIEW PROJECT

- Nausea
  - Pramlintide plus insulin (range: 47%-95%) > placebo plus insulin (range: 12%-36%)
- Severe nausea
  - Pramlintide plus insulin (range: 6%-9%) > placebo plus insulin (range:1%-2%)
- Patients who did not tolerate pramlintide 60 µg dose also experienced nausea with 30 µg dose
- Vomiting
  - Pramlintide plus insulin (>10%) > placebo plus insulin (up to 8%)
- Severe vomiting
  - Pramlintide plus insulin (up to 2%) ≈ placebo plus insulin (0.7%)
- 2 trials reported that most cases of nausea and vomiting occurred within 2-4 weeks of treatment; however, data were not provided in the studies to verify the statements

# Harms

DRUG EFFECTIVENESS REVIEW PROJECT

- Anorexia or reduced appetite
  - Overall, pramlintide plus insulin (11%-18%) > placebo plus insulin (2%-3%)
- Severe anorexia or reduced appetite
  - Less than 2% of pramlintide-treated patients experienced this event compared with 0% of placebo-treated patients
- Sinusitis
  - Pramlintide plus insulin (14%) ≈ placebo plus insulin (9%)

# Subgroups

DRUG EFFECTIVENESS REVIEW PROJECT

- Body mass index
  - Data reported for week 26 instead of week 52
  - Baseline body mass index ≤ 23 kg/m$^2$ (lean patients):
    - Pramlintide appeared to “inhibit” weight gain
  - Baseline body mass index >23 kg/m$^2$ (obese patients):
    - Pramlintide produced mild weight loss (approximately -1 to -2 kg)
- Baseline A1c ≤ 8.5%
  - Change in A1c and change in weight were not different from patients with A1c ≥ 8.5% and there was no ↑ risk of hypoglycemia
- Stable insulin dose
  - Treatment effect in lowering A1c was greater in patients on stable insulin doses (no more than ±10% change in total daily dose) than patients who may or may not have abided by stringent guidelines
  - Generalizability of using fixed doses of insulin in clinical practice is limited

# Generalizability

DRUG EFFECTIVENESS REVIEW PROJECT

- Methods of patient recruitment not reported
- Baseline comorbid conditions not specified
- Included subjects likely represent highly selected population:
  - White middle-aged adults
  - Baseline A1c: 8%-9%
  - Duration of diabetes: 16-21 years
  - High motivation to administer additional 2-4 injections on top of current insulin regimen and to increase frequency of self-monitoring of glucose
- Included patients did not have significant cardiovascular, renal, or gastrointestinal motility problems
- Study setting: Not reported, but likely clinic

# Pramlintide: Key questions 2 and 3

DRUG EFFECTIVENESS REVIEW PROJECT

2. For children and adults with **type 2 diabetes** does pramlintide differ in efficacy, effectiveness, or harms in achieving glycemic control when added to insulin compared with conventional insulin therapy with or without concurrent oral hypoglycemic agents?

3. Are there subgroups of patients for which pramlintide is more or less suitable than other hypoglycemic agents?

# Results

DRUG EFFECTIVENESS REVIEW PROJECT

- Addition of pramlintide to *flexible-dose* glargine without prandial insulin ± oral hypoglycemic agents
  - Pramlintide 60 µg or 120 µg (before meals, two to three times daily) plus glargine ± oral hypoglycemia agents was slightly more effective than placebo plus glargine in lowering A1c, weight, and postprandial glucose (1 short-term trial)
  - No significant difference in total daily insulin dose adjustments between treatment groups (1 short-term trial)
  - No significant difference in percent achieving A1c <7% (1 short-term trial)

# Intermediate outcomes: *Flexible-dose* insulin

DRUG EFFECTIVENESS REVIEW PROJECT

| | Riddle, 2007[a] | |
|---|---|---|
| | **Pramlintide 60-120 µg BID-TID** | **Placebo** |
| A1c | **-0.70%**[b] | -0.34% |
| Weight | -1.6 kg | +0.7 kg |
| Postprandial glucose | -24.4 mg/dL | -0.4 mg/dL |
| Total daily insulin dose | +11.7 units | +13.1 units |

Abbreviations: BID, twice a day; TID, three times a day.

[a] Glargine was adjusted to achieve prespecified fasting glucose targets after pramlintide doses were stabilized;16 weeks duration.

[b] $P<0.005$ compared with placebo

# Results

DRUG EFFECTIVENESS REVIEW PROJECT

- Addition of pramlintide to *fixed- or stable-dose* insulin ± oral hypoglycemic agents
  - Pramlintide 75 µg, 90 µg, 120 µg, and 150 µg plus fixed dose insulin ± oral hypoglycemic agents was slightly more effective than placebo plus insulin in reducing A1c and weight (2 trials)
  - Changes in total daily insulin dose were not significantly different between treatment groups (2 trials)
  - About 9%-19% of pramlintide-treated patients achieved A1c <7% compared with 4%-11% of placebo-treated patients (2 trials)

# Intermediate outcomes: *Fixed-or stable dose* insulin

DRUG EFFECTIVENESS REVIEW PROJECT

| Ratner, 2002[a] | | | |
|---|---|---|---|
| | **Pramlintide 75 µg TID** | **Pramlintide 150 µg TID** | **Placebo** |
| A1c | -0.5% | **-0.6%*** | -0.2% |
| Weight | -0.5 kg | **-1.4 kg*** | +1.0 kg |
| Total insulin dose | +10.9% | +7.9% | +8.1% |

| Hollander, 2003[b] | | | |
|---|---|---|---|
| | **Pramlintide 90 µg BID** | **Pramlintide 120 µg BID** | **Placebo** |
| A1c | -0.35% | **-0.62%**** | -0.22% |
| Weight | **-0.5 kg**** | **-1.25 kg**** | +0.6 kg |
| Total insulin dose | +2 units | +1 unit | +2 units |

Abbreviations: BID, twice a day; TID, three times a day.
[a] 52 weeks in duration
[b] 52 weeks in duration
*$P<0.01$, between-group difference with placebo
**$P<0.05$ compared with placebo

# Withdrawals and harms

DRUG EFFECTIVENESS REVIEW PROJECT

- Withdrawal due to all causes and withdrawal due to adverse events
  - Pramlintide plus insulin ± oral hypoglycemic agents ≈ placebo plus insulin ± oral hypoglycemic agents
- No significant cardiac, hepatic, renal, or drug-related idiosyncratic adverse events were observed in any treatment group
- None of the included studies reported anorexia, reduced appetite, vomiting, or death

# Harms

DRUG EFFECTIVENESS REVIEW PROJECT

- Hypoglycemia
  - Pramlintide plus insulin ± oral hypoglycemic agents ≈ placebo plus insulin ± oral hypoglycemic agents
  - Severe:
    - Pramlintide plus insulin ± oral hypoglycemic agents slightly > placebo plus insulin ± oral hypoglycemic agents
    - Higher rates during first 4 weeks of treatment and especially with higher doses (> 120 µg)
- Nausea
  - Mild to moderate:
    - Pramlintide plus insulin ± oral hypoglycemic agents (16%-31%) > placebo plus insulin ± oral hypoglycemic agents (3%-17%)
  - Severe: slightly ↑ with pramlintide
- Headaches
  - Conflicting results in 2 trials: 1 study showed a higher rate with pramlintide than with placebo; another study showed no difference
  - None of the trials assessed whether there was a correlation between headache and hypoglycemia

# Subgroups

DRUG EFFECTIVENESS REVIEW PROJECT

- Nausea and weight loss
  - Weight loss with pramlintide 90 or 120 µg appeared to be independent of nausea
    - Never experiencing nausea (change in weight: -1.1 to -1.5 kg) compared with experiencing nausea at anytime (change in weight: -0.3 to -2.0 kg)
- Weight loss and A1c
  - Improvements in A1c with pramlintide appeared to be independent of weight lost or gained
    - Subjects who gained weight change in A1c: -0.29% to -0.53%; subjects who lost weight change in A1c: -0.22% to -0.58%
- Body mass index
  - At 26 weeks, patients with body mass index >25 kg/m$^2$ showed largest ↓ in A1c and weight with pramlintide than with placebo
    - Approximately 2% of these patients achieved clinically relevant weight loss of >10% of their weight from baseline

# Subgroups

DRUG EFFECTIVENESS REVIEW PROJECT

- Baseline A1c
  - Patients with baseline A1c >8.5% showed larger reductions in A1c (-1.19%) than patients with baseline A1c ≤ 8.5% (-0.36%)
- Race and ethnicity
  - Black patients had larger treatment effects in lowering A1c and weight than White or Hispanic patients
    - Black and Hispanic patients had slightly higher baseline A1c than White patients (baseline A1c 9.2%-9.7% compared with 8.9%-9.1%)
    - Change in A1c and weight: among blacks, -0.7%, -4.1 kg; whites, -0.5%, -2.4 kg; and Hispanics, -0.3%, -2.3 kg

# Generalizability

DRUG EFFECTIVENESS REVIEW PROJECT

- None of the trials evaluated pramlintide in patients who were inadequately managed on insulin plus oral hypoglycemic therapy
- Baseline comorbid conditions were rarely specified
- Included study patients represent a highly selected population
  - White middle-aged adults
  - Baseline A1c 8.5%-9.0%
  - Duration of diabetes 11-13 years
  - High motivation to administer additional 2-3 injections on top of current regimen of insulin plus oral hypoglycemic
- Included patients did not have significant cardiovascular, renal, or gastrointestinal problems at baseline
- Study setting: not reported but likely clinic

# Exenatide

# Results from 1 systematic review

DRUG EFFECTIVENESS REVIEW PROJECT

- Amori 2007
  - High-quality
  - Exenatide compared with placebo:
    - A1c: -1.01% (95% CI -1.18 to -0.84)
    - Fasting plasma glucose: -17 mg/dL (95% CI -34 to -20)
    - Weight: -1.44 kg (95% CI -2.13 to -0.75)
  - Exenatide compared with insulin:
    - A1c: no significant difference
    - Fasting plasma glucose: no significant difference
    - Weight: -4.8 kg (95% CI -6.0 to -3.5)
  - Adverse events: hypoglycemia (rarely severe), nausea, vomiting, and diarrhea

# Exenatide: Key question 1

DRUG EFFECTIVENESS REVIEW PROJECT

For children and adults with type 2 diabetes does exenatide differ in efficacy, effectiveness, or harms in achieving glycemic control **compared with other hypoglycemic agents as monotherapy or combined therapy**?

## Results

- No studies meeting inclusion criteria compared exenatide with oral diabetes agents as either monotherapy or combined therapy

# Exenatide: Key question 2

DRUG EFFECTIVENESS REVIEW PROJECT

For children and adults with type 2 diabetes, does exenatide differ in efficacy, effectiveness, or harms in achieving glycemic control **when added to other hypoglycemic agents compared with conventional insulin therapy**?

# Results

DRUG EFFECTIVENESS REVIEW PROJECT

- Exenatide or insulin with metformin and/or sulfonylurea (4 active-controlled trials)
  - 3 randomized controlled trials
    - A1c: ↓ both groups, nonsignificant between groups
    - Weight: ↑ with insulin, ↓ with exenatide
  - 1 exploratory substitution study
    - Substitution of exenatide for insulin did not improve A1c compared with those on insulin + metformin and/or sulfonylurea

# Results

DRUG EFFECTIVENESS REVIEW PROJECT

- Exenatide compared with placebo
  - Between-group changes (4 placebo-controlled trials):
    - A1c
      - 5 µg twice daily: -0.59 (95% CI -0.79 to -0.40)
      - 10 µg twice daily: -0.97% (95% CI -1.16 to -0.79)
    - Fasting plasma glucose
      - 10 mcg twice daily: -1.50 mmol/L (95% CI -1.85 to -1.15)
    - Weight
      - 10 µg twice daily: -1.25 kg (95% CI -1.90 to -0.61)

# Results

DRUG EFFECTIVENESS REVIEW PROJECT

- Quality of life
  - No significant differences between exenatide twice daily and insulin glargine, despite higher rates of gastrointestinal adverse effects with exenatide (1 study)

# Withdrawals and harms

DRUG EFFECTIVENESS REVIEW PROJECT

- Withdrawal due to all causes
  - Exenatide > insulin
  - Exenatide 5 µg twice daily < placebo
  - Exenatide 10 µg twice daily = placebo
- Withdrawals due to adverse events
  - Exenatide 10 µg twice daily > placebo
  - Exenatide 5 µg twice daily = placebo
- Hypoglycemia
  - Exenatide = insulin; ↑ with sulfonylurea or metformin
  - Exenatide 10 µg twice daily > placebo (relative risk 2.4, 95% CI 1.1 to 5.5)
  - Exenatide 5 µg twice daily > placebo ($P$>0.05)

# Harms

DRUG EFFECTIVENESS REVIEW PROJECT

- Nausea
  - Exenatide 10 µg twice daily compared with placebo: relative risk 2.8 (95% CI 1.9 to 4.3)
- Diarrhea
  - Exenatide 10 µg twice daily compared with placebo: relative risk 2.4 (95% CI 1.6 to 3.5)
- No evidence of cardiovascular, pulmonary, hepatic, or renal adverse effects. Rates of serious events were similar between treatment groups.

# Exenatide: Key question 3

DRUG EFFECTIVENESS REVIEW PROJECT

Are there subgroups of patients for which exenatide is more or less suitable than other hypoglycemic agents?

# Subgroups

DRUG EFFECTIVENESS REVIEW PROJECT

- Age
  - Exenatide equally efficacious in reducing A1c in subjects > or < 65 years of age (1 pooled analysis)
  - Rates of hypoglycemia similar between those > or < 65 years of age (1 pooled analysis)
- No other data on subgroups defined by demographic or other characteristics

# Generalizability

DRUG EFFECTIVENESS REVIEW PROJECT

- Included studies were small and the populations were generally homogeneous and highly selected
- Significant comorbidities were excluded
- The number of patients who did not meet run-in requirements was generally not reported and reasons for exclusion were not specified
- Open-label extension studies involved highly selected populations of patients who completed the primary trial and volunteered to continue with (or start) on exenatide

# Sitagliptin

# Results from 1 systematic review


- Sitagliptin (8 studies) and vildagliptin (12 studies) were reviewed together
- Sitagliptin monotherapy compared with other oral hypoglycemic agents monotherapy
  - Weighted mean difference, A1c: +0.21% (95% CI 0.02 to 0.39)
- Sitagliptin monotherapy or added as combined therapy compared with placebo
  - Weighted mean difference, A1c: -0.74% (95% CI -0.84 to -0.63)
  - Weighted mean difference, fasting plasma glucose: -22 mg/dL (95% CI -26 to -18)
  - Weighted mean difference, weight: +0.52 kg (95% CI 0.28 to 0.76)
- Sitagliptin was generally well tolerated

# Sitagliptin: Key question 1

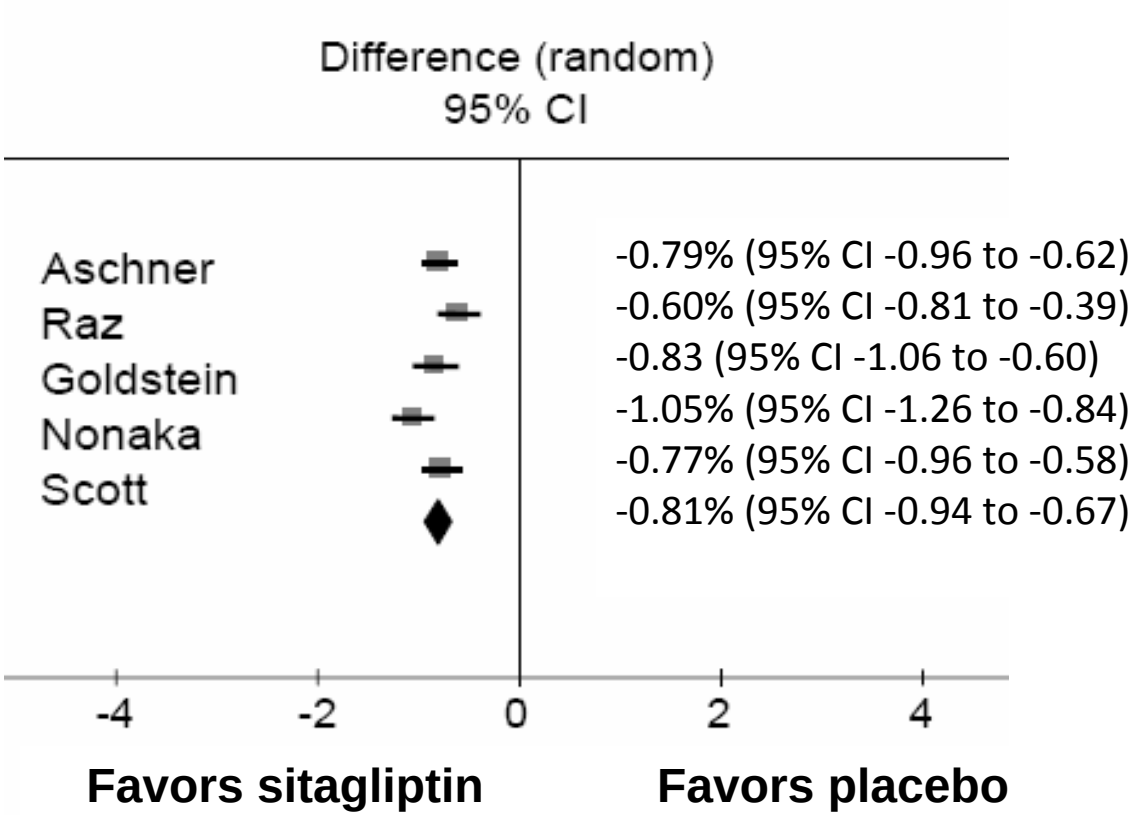
DRUG EFFECTIVENESS REVIEW PROJECT

For children and adults with type 2 diabetes does sitagliptin differ in efficacy, effectiveness, or harms in achieving glycemic control **compared with placebo**?

# Results

DRUG EFFECTIVENESS REVIEW PROJECT

- Sitagliptin monotherapy compared with placebo
  - Meta-analysis of change in A1c



# Results


- Moderate reductions in fasting plasma glucose and postprandial glucose (pooled 5 trials)
  - Fasting plasma glucose -24 mg/dL (95% CI -29.5 to -19.3)
  - Postprandial glucose -55 mg/dL (95% CI -65.5 to -43.3)
- Weight loss occurred in sitagliptin and placebo groups but patients on sitagliptin lost less weight (5 trials)
  - Pooled estimate: 0.62 kg (95% CI 0.36 to 0.89)

# Sitagliptin: Key question 2

DRUG EFFECTIVENESS REVIEW PROJECT

For children and adults with type 2 diabetes does sitagliptin differ in efficacy, effectiveness, or harms in achieving glycemic control **as monotherapy compared with other hypoglycemic agents or when added as part of combined therapy**?

# Results

DRUG EFFECTIVENESS REVIEW PROJECT

- Sitagliptin monotherapy compared with other hypoglycemic agents
  - Patients on glipizide 5-20 mg daily or metformin 1-2 g daily showed numerically larger reductions in A1c, fasting plasma glucose, and postprandial glucose than sitagliptin monotherapy
  - However, based on the magnitude of difference between sitagliptin and glipizide or metformin, it appears that sitagliptin may be comparable to glipizide (+0.22%) or metformin 1g daily (+0.16%)
  - The magnitude of difference between sitagliptin and metformin 2 g daily was larger (+0.47%), and it is unclear whether the difference would have achieved statistical significance if analyses were conducted

# Intermediate outcomes: Sitagliptin compared with glipizide or metformin

DRUG EFFECTIVENESS REVIEW PROJECT

| | Scott, 2007[a] | | Goldstein, 2007[b] | | |
|---|---|---|---|---|---|
| | Sitagliptin 100 mg daily | Glipizide 5-20 mg daily | Sitagliptin 100 mg daily | Metformin 1 g daily | Metformin 2 g daily |
| A1c | -0.54% | -0.76% | -0.66% | -0.82% | -1.13% |
| FPG (mg/dL) | -18.2 | -24.8 | -17.5 | -27.3 | -29.3 |
| PPG (mg/dL) | -48.4 | -66.4 | -51.9 | -53.4 | -78.0 |
| Weight | +0.4 kg | +0.9 kg | 0.0 kg | -0.9 kg | -1.1 kg |

Abbreviations: FPG, fasting plasma glucose; PPG, postprandial glucose.

[a] Noninferiority trial, analysis based on per protocol results are presented; 12 weeks in duration

[b] This trial included additional treatment arms that are not presented in this table; 24 weeks in duration

# Results

DRUG EFFECTIVENESS REVIEW PROJECT

- Sitagliptin added as combined therapy
  - In patients inadequately controlled on metformin, addition of sitagliptin was as effective as addition of glipizide or rosiglitazone in lowering A1c and weight (2 trials)
    - Change in A1c: sitagliptin -0.67% compared with glipizide -0.67% (Nauck, 2007)
    - Change in A1c: sitagliptin -0.51% compared with rosiglitazone -0.57% (Scott, 2008)
  - In patients inadequately controlled on metformin, pioglitazone, rosiglitazone, or glimepiride, the addition of sitagliptin significantly reduced A1c and fasting plasma glucose compared with placebo (4 trials)

# Results

DRUG EFFECTIVENESS REVIEW PROJECT

- Sitagliptin added as combined therapy (continued)
  - In patients inadequately controlled on glimepiride plus metformin, the addition of sitagliptin significantly improved A1c, fasting plasma glucose, and postprandial glucose compared with placebo

| | **Hermansen, 2006** | |
|---|---|---|
| | **Sitagliptin+ glimepiride+metformin[a]** | **Placebo+ glimepiride+metformin[b]** |
| A1c | **-0.59%[c]** | +0.3% |
| FPG | **-7.8 mg/dL[c]** | +12.9 mg/dL |
| PPG | **-21.3 mg/dL[c]** | +15.8 mg/dL |

Abbreviations: FPG, fasting plasma glucose; PPG, postprandial glucose.
[a] Sitagliptin 100 mg/d + glimepiride 4-8 mg/d + metformin 1500-3000 mg/d.
[b] Placebo + glimepiried 4-8 mg/d + metformin 1500-3000 mg/d.
[c] Between-group differences were statistically significant for all of the reported outcomes ($P<0.05$ or $P<0.01$).

# Results

DRUG EFFECTIVENESS REVIEW PROJECT

- Sitagliptin added as combined therapy (continued)
  - In patients inadequately controlled on diet and exercise, the addition of sitagliptin plus metformin was more effective than the addition of sitagliptin monotherapy or metformin monotherapy

| | Goldstein, 2007[a] | | | | |
|---|---|---|---|---|---|
| | **Sitagliptin+ met 1g daily[b]** | **Sitagliptin+ met 2g daily[b]** | **Met 1g daily** | **Met 2 g daily** | **Sitagliptin** |
| A1c | **-1.4%** | **-1.9%** | -0.82% | -1.13% | -0.66% |
| FPG (mg/dL) | **-47.1** | **-63.9** | -27.3 | -29.3 | -17.5 |
| PPG (mg/dL) | **-92.5** | **-116.6** | -53.4 | -78.0 | -51.9 |

Abbreviations: FPG, fasting plasma glucose; met, metformin; PPG, postprandial glucose.
[a] This trial included additional treatment arms which are not presented here; 24 weeks in duration.
[b] $P<0.001$ compared with sitagliptin monotherapy or metformin monotherapy for A1c, FPG, PPG.

# Withdrawals and harms

DRUG EFFECTIVENESS REVIEW PROJECT

- Withdrawal due to all causes and withdrawal due to adverse events
  - Sitagliptin monotherapy < placebo
    - Total withdrawal: pooled relative risk 0.69, 95% CI 0.55-0.88
    - Due to adverse events: pooled relative risk 0.76, 95% CI 0.33-1.73
  - Sitagliptin added as combined therapy slightly > metformin, pioglitazone, glimepiride monotherapy
- Commonly reported adverse events with sitagliptin were hypoglycemia, abdominal pain, nausea, and diarrhea
  - 90% of severe hypoglycemia occurred in patients on glipizide monotherapy or as combined therapy with sitagliptin
  - Minimal risk of mild-moderate hypoglycemia associated with sitagliptin monotherapy compared with placebo (pooled relative risk 1.21, 95% CI 0.42-3.5)
  - No statistically significant difference in abdominal pain, nausea, and diarrhea when sitagliptin was compared with placebo
  - When sitagliptin was combined with glimepiride, metformin, pioglitazone, or metformin, the rate for abdominal pain, nausea, and diarrhea was <6%

# Harms

DRUG EFFECTIVENESS REVIEW PROJECT

- 5 trials reported “rare” adverse events
  - Occurring at least 4%: upper respiratory tract infections, headaches, influenza, nasopharyngitis, and urinary tract infections
- 4 trials reported small increases in mean white blood cell count (≤10% from baseline)
  - Increases were mainly in absolute neutrophil count; occurred early and remained stable

# Sitagliptin: Key question 3

DRUG EFFECTIVENESS REVIEW PROJECT

Are there subgroups of patients for which sitagliptin is more or less suitable than other hypoglycemic agents?

# Subgroups

DRUG EFFECTIVENESS REVIEW PROJECT

- Age, sex, race, and body mass index
  - No significant differences in A1c based on these subgroups (7 trials)
  - Hispanic patients exhibited largest ↓ in A1c followed by white patients and “other” patients (from data on file from 1 trial)
- Baseline A1c
  - Larger ↓ in A1c in patients with baseline A1c ≥9% than in patients with baseline A1c <8% (2 trials)
  - 4 trials did not observe any significant differences based on baseline A1c
- Duration of diabetes
  - Patients with ≤3 years’ duration of diabetes had greater improvement in A1c than patients with >3 years' duration of diabetes (1 trial)

# Generalizability

DRUG EFFECTIVENESS REVIEW PROJECT

- Method of recruitment not reported
- Highly selected population
  - Long dose-stabilization and run-in periods in which patients with >75% adherence were randomized to treatments
  - Enrolled patients were mainly obese white adults with moderately elevated A1c (generally <9% at baseline)
  - Duration of diabetes <10 years
- Baseline information on comorbid conditions and other disease specific characteristics were not specified

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