Annals of Internal Medicine | Review

Meta-Analysis: Efficacy and Safety of Inhaled Insulin Therapy in Adults with Diabetes Mellitus

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Background: Injection insulin therapy is not readily accepted by patients and many health care providers; therefore, less invasive options for insulin therapy are desirable.

Purpose: To examine the efficacy, safety, and patient acceptability of inhaled insulin therapy in nonpregnant adults with diabetes mellitus.

Data Sources: English-language studies in MEDLINE, the Cochrane Clinical Trials Register (through June 2006), and U.S. Food and Drug Administration review documents of the first formulation of inhaled insulin approved for clinical use.

Study Selection: Randomized, controlled trials of at least 12 weeks' duration that compared inhaled insulin with another active therapy and reported hemoglobin A_{1c} levels in adults with type 1 or type 2 diabetes mellitus.

Data Extraction: Two reviewers independently assessed trials for inclusion and extracted data. Differences were resolved by consensus.

Data Synthesis: Sixteen open-label trials met the inclusion criteria (4023 patients; age range, 18 to 80 years). Among patients with type 1 or type 2 diabetes, there was a small decrease in hemoglobin A_{1c} level from baseline that favored subcutaneous insulin over inhaled insulin (weighted mean difference, 0.08% [95% CI, 0.03% to 0.14%]), although there was no difference in the proportion of participants achieving hemoglobin A_{1c} levels less than 7%. Inhaled insulin lowered hemoglobin A_{1c} levels more (weighted mean difference favoring inhaled insulin, −1.45% [CI, −1.80% to − 1.10%]) compared with fixed doses of oral agents but much less when compared with oral agents titrated to glycemic efficacy (weighted mean difference favoring inhaled insulin, −0.20% [CI, −0.34% to − 0.07%]). Severe hypoglycemia was more likely to occur with inhaled insulin than with oral agents (risk ratio, 3.1 [CI, 1.0 to 9.1]), but there was no increased risk compared with subcutaneous insulin. There was an increased incidence of mild to moderate nonprogressive dry cough in patients treated with inhaled insulin (risk ratio, 3.5 [CI, 2.2 to 5.6]) and a mild decrease in certain pulmonary function testing variables, which did not progress over 2 years. Patients preferred inhaled insulin over subcutaneous insulin.

Limitations: All trials were open label, which may introduce bias. Most of the trials were of 24 weeks' duration or less, limiting assessment of long-term safety.

Conclusions: Inhaled insulin offers an alternative noninvasive option for premeal insulin administration, with glycemic efficacy slightly less than subcutaneous regular insulin and increased patient acceptability. Until long-term safety data are available, inhaled insulin should be reserved for nonpregnant adults with diabetes who are opposed to injections and who would otherwise delay appropriate and timely therapy with insulin.

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Despite the availability of effective diabetes-specific therapies, achievement of glycemic goals in patients with diabetes is far from adequate in the United States: Fewer than half of adults with diabetes attain a hemoglobin A_{1c} level less than 7% (1, 2). Insulin is effective at lowering hyperglycemia, but there is considerable resistance to its use by patients and health care providers, primarily because of the need for subcutaneous injection (3, 4); thus, patients may defer initiating insulin therapy for prolonged periods. Alternative and less invasive options for insulin therapy are therefore desirable. On 27 January 2006, the U.S. Food and Drug Administration (FDA) approved the first formulation of inhaled insulin for clinical use in nonsmoking adults with type 1 or type 2 diabetes and no pulmonary disease (5), offering the first new delivery option for insulin since its discovery in the 1920s.

Because of its pharmacokinetic profile (6), inhaled insulin has been studied as a premeal noninvasive alternative to subcutaneous regular insulin or rapid-acting insulin. A previous systematic review of clinical trials comparing inhaled insulin with subcutaneous insulin included 6 studies, 4 of which were published in abstract form; only 3 studies provided sufficient data to allow meta-analysis (7). Since this publication, additional trials have published data on the efficacy and safety of inhaled insulin versus subcutaneous insulin in patients with type 1 or type 2 diabetes or inhaled insulin versus oral hypoglycemic agents in patients with type 2 diabetes. The objective of the present systematic review was to examine the efficacy, safety, and patient acceptability of inhaled insulin therapy in nonpregnant adults with diabetes.

Methods

Data Sources and Searches

We conducted a systematic search of MEDLINE (from 1966 through 22 June 2006) and the Cochrane Controlled Clinical Trials Register (from the second quar-

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Context

Is inhaled insulin therapy a reasonable alternative to other hypoglycemic agents?

Contribution

This systematic review of 16 randomized trials in adult patients with type 1 or type 2 diabetes found that inhaled insulin reduced hemoglobin A_{1c} levels slightly less than subcutaneous insulin and more than fixed doses of oral agents. Patients preferred inhaled insulin over subcutaneous insulin. Severe hypoglycemia was more likely with inhaled insulin than with oral agents. Inhaled insulin caused mild to moderate nonprogressive dry cough and mild decreases in pulmonary function in some patients.

Cautions

All trials were open label. Most were less than 6 months in duration.

—The Editors

ter of 2006) to find English-language randomized, controlled trials (parallel or crossover) of inhaled insulin in nonpregnant adults with diabetes. We used the following search terms: *diabetes, blood sugar, hyperglycemia, glucose, glycohemoglobin, hemoglobin A1c, inhaled, inhalation, aerosol, pulmonary, insulin, human,* and *clinical trial*. We searched for additional publications in personal reference lists and citation sections of recovered articles. We excluded letters, abstracts, and conference proceedings that were not published in full in peer-reviewed journals because discrepancies are common between meeting abstract results and subsequent publication results (8). To find unpublished studies of inhaled insulin, we also reviewed the briefing document on Exubera (recombinant DNA origin) powder for oral inhalation (Pfizer Inc., New York, New York) (9), which was released under public disclosure laws for the FDA advisory committee meeting on 8 September 2005.

Study Selection

Two reviewers independently screened abstracts according to the inclusion criteria. An abstract was judged relevant if it reported original data from controlled trials in patients with type 1 or type 2 diabetes and hemoglobin A_{1c} outcomes for patients receiving inhaled insulin therapy versus outcomes for a comparison group (subcutaneous insulin or oral hypoglycemic agents). We excluded studies of less than 12 weeks' duration because they would provide an inadequate assessment of change in glycemic efficacy; hemoglobin A_{1c} levels reflect glycemia over the previous 3 months (10). Full-text articles were retrieved and reviewed if a decision regarding inclusion could not be made solely on the basis of the abstract. Any discrepancies were resolved by consensus between the 2 independent reviewers or in group conference by referencing the original article. Both reviewers also screened for unpublished controlled trials listed in the briefing document on Exubera (9).

Data Extraction and Quality Assessment

From the included studies, we extracted participants' baseline characteristics, including types of interventions. For glycemic efficacy, we extracted data on change in hemoglobin A_{1c} level from baseline and the proportion of patients achieving hemoglobin A_{1c} levels less than 7%. We also gathered nonglycemic outcomes, such as change in body weight and overall patient satisfaction. To evaluate safety, we extracted data on severe hypoglycemia, pulmonary symptoms, change in pulmonary function, and level of circulating insulin antibodies. Because combining the total number of hypoglycemic events does not account for recurrent events in the same patient, we combined data on the total number of patients per treatment group who reported at least 1 episode of severe hypoglycemia. Because of the varied methods of reporting hypoglycemia in individual trials, we used the FDA definition (patient had a blood glucose level $\leq$2 mmol/L [$\leq$36 mg/dL] or required assistance) when available (9). We did not collect data on fasting or postprandial glucose values, because they were self-reported and therefore were less reliable than hemoglobin A_{1c} levels. Moreover, fasting glucose values reflect the effectiveness of the long-acting basal insulin regimen (11) rather than inhaled insulin, which was given with meals.

All included studies were open label; therefore, we used the following features to assess study quality: allocation generation (proper randomization), intention-to-treat analysis, dropout rate, and whether the study was designed for glycemic efficacy "noninferiority" or "superiority") or safety. For trials with duplicate publications, the most complete or updated publication was eligible for consideration. We contacted the first author of 1 study (12) to confirm that it was an independent trial. Data extraction from the published reports was supplemented by using publicly available information (9).

Data Synthesis and Analysis

For glycemic efficacy, the primary measure was the treatment group difference in the change in hemoglobin A_{1c} level from baseline. The secondary outcome was the proportion of participants achieving hemoglobin A_{1c} levels less than 7%. For safety, we examined the number of participants reporting severe hypoglycemia and cough and treatment group difference in changes in pulmonary function variables (FEV_1 and diffusing capacity of carbon monoxide [DL_{CO}]).

For continuous variables (hemoglobin A_{1c} level, FEV_1, and DL_{CO}), we calculated the weighted mean difference and 95% CI for change from baseline in the inhaled insulin group versus the comparison group (subcutaneous insulin or oral hypoglycemic agent). For dichotomous variables (the proportion of patients achieving hemoglobin A_{1c} levels $<$7%, the proportion with severe hypoglycemia, and the proportion with cough), we calculated the risk ratio

and CI for the inhaled insulin group versus the comparison group (subcutaneous insulin or oral hypoglycemic agent). When appropriate, we combined data from all studies in patients with type 1 or type 2 diabetes and explored heterogeneity between comparable trials: Subgroup analysis was done by using type of diabetes, type of treatment (subcutaneous insulin or oral hypoglycemic agent), and duration of intervention.

For nonglycemic outcomes, such as change in weight, insulin antibodies, and patient satisfaction, we did not perform meta-analyses because of insufficient reported data on variance for a quantitative analysis. However, we performed meta-analyses of weight change between patients receiving inhaled insulin and those receiving oral hypoglycemic agents because data were available. For all meta-analyses, we used a random-effects model that weighed studies by the inverse of the within-study and between-study variances (13). When available, we used data obtained from intention-to-treat analyses as presented elsewhere (9). Most studies reported the difference of the mean change and the corresponding CI (or standard error) between comparison groups. For studies that reported only the mean changes and the corresponding standard errors of the mean change, we calculated the difference and the standard errors of the difference between comparison groups using these data. We used the I^2 statistic to quantify the degree of heterogeneity among trials in each meta-analysis (14).

Role of the Funding Sources

The funding sources, National Institutes of Health and Friedman Foundation, had no role in the design, conduct, or reporting of the study or in the decision to submit the manuscript for publication.

Results

Search Results

The **Appendix Figure** (available at www.annals.org) summarizes the search results, and the **Table** summarizes the characteristics of the 16 trials (9, 12, 15–25) included in the review.

Patient Characteristics and Description of Interventions

The 16 included trials involved 4023 participants (42% women and 86% white) (**Table**). Baseline hemoglobin A_{1c} levels ranged from 7% to 9.8%, and body mass index ranged from 24 kg/m^2 to 32 kg/m^2. Seven trials (9, 12, 15, 20, 23, 25) compared inhaled insulin with subcutaneous regular insulin, insulin lispro, or insulin aspart in patients with type 1 diabetes (1534 participants; age range, 18 to 65 years). Eight trials with 9 treatment groups compared inhaled insulin with subcutaneous regular insulin (9, 16, 18, 19) or oral hypoglycemic agents (9, 17, 21, 22, 24) in patients with type 2 diabetes (2489 participants; age range, 30 to 80 years). The subcutaneous insulin regimens in the comparison groups included a combination of basal (neutral protamine Hagedorn insulin, ultralente insulin, or insulin glargine given once or twice daily) and bolus (regular insulin or insulin lispro or insulin aspart given 2 or 3 times daily) insulin (**Table**). Oral hypoglycemic regimens included all of the common classes (sulfonylureas, metformin, and thiazolidinediones) taken either alone or in combination with 1 or 2 other oral medications (**Table**). One study included medication-naive patients (21). Inhaled insulin was administered with meals and was titrated according to study-specific glucose goals. Subcutaneous insulin used as a control was also titrated to glucose goals identical to those of inhaled insulin. Doses of oral hypoglycemic agents were not adjusted to glycemic targets, with the exception of 2 trials that titrated the oral medication dose to achieve maximum glycemic efficacy (9, 24).

Methodologic Quality

All trials were open label, and none reported whether the investigators involved in data collection or analyses were blinded to participant information regarding treatment assignment. No studies used the "double-dummy" technique, in which all patients receive an inhaler and injections (with only 1 of the 2 methods delivering active study drug or placebo), because it was thought to be logistically difficult and cumbersome. All trials comparing inhaled insulin with subcutaneous insulin were designed for "noninferiority" whereas those comparing inhaled insulin with oral agents were designed to show "superiority" of inhaled insulin. Seven of the 12 published studies (15, 17, 18, 21, 22, 24, 25) presented an intention-to-treat analysis, whereas the remaining studies presented a per protocol analysis. However, data were available from intention-to-treat analyses of the Exubera studies (9) and were used in the meta-analyses. Pharmaceutical companies funded all studies; however, the role of the funding source was clearly disclosed in only 1 study (22).

Glycemic Outcomes

Inhaled versus Subcutaneous Insulin

When we combined data from studies that compared inhaled insulin and subcutaneous insulin in patients with type 1 or type 2 diabetes, there was a small but statistically significant difference in the decrease in hemoglobin A_{1c} levels from baseline favoring subcutaneous insulin (weighted mean difference, 0.08% [CI, 0.03% to 0.14%]) (**Figure 1**). The advantage of subcutaneous insulin over inhaled insulin was evident in the 2 studies of 104 weeks' duration (9) (weighted mean difference, 0.18% [CI, 0.09% to 0.27%]) (**Figure 1**) although there was no difference between subcutaneous insulin versus inhaled insulin in studies of less than 24 weeks' duration.

Among the 5 trials (18–20, 23, 25) that provided data on the number of patients with type 1 or type 2 diabetes who achieved hemoglobin A_{1c} levels less than 7%, there was no difference between the inhaled and subcutaneous insulin groups in the proportion achieving this goal (risk

Table. **Characteristics of Randomized, Controlled Trials of Inhaled Insulin Included in the Systematic Review***

Study, Year (Reference)	Study Duration, *wk*	Participants, *n*	Mean Age (Range), *y*	Women, %	White, %	Duration of Diabetes, *y*	Baseline Hemoglobin A_{1c} Level, %
Type 1 diabetes (inhaled vs. subcutaneous insulin)							
Skyler et al., 2001 (15)	12	72	37 (18–55)	47	81	14.5	8.5
Quattrin et al., 2004 (20)	24	268†	33 (18–36)	46	90	16	8.3
Skyler et al., 2005 (23)	24	206†	29 (18–65)	47	90	13	8.2
Heise et al., 2005 (12)	24	45	36 (18–50)	NR	NR	17	7
Exubera study 1022, 2005 (9)	104	580	NR (18–65)	NR	NR	NR	7.5
Exubera study 1027, 2005 (9)	24	226	NR (25–65)	NR	NR	NR	7.6
Garg et al., 2006 (25)	12	137	39 (26–53)	53	88	>1	8.1
Type 2 diabetes (inhaled vs. subcutaneous insulin)							
Cappelleri et al., 2002 (16)	12	56	52 (35–65)	39	53	11	‡
Hermansen et al., 2004 (18)	12	107	59 (30–75)	37	§	12	8.5
Hollander et al., 2004 (19)	24	298	57 (35–80)	33	76	14	8.5
Exubera study 1029, 2005 (9)	104	625	NR (35–75)	NR	NR	NR	7.8
Type 2 diabetes (inhaled vs. oral hypoglycemic agents)							
Weiss et al., 2003 (17)	12	69	51 (35–65)	35	64	8	9.8
Rosenstock et al., 2005 (22)‖	12	298	57 (35–80)	34	80	9	9.5
DeFronzo et al., 2005 (21)	12	143	54 (35–80)	45	74	4	9
Barnett et al., 2006 (24)	24	423	60 (35–80)	47	96	9	9.7
Exubera study 1002, 2005 (9)	24	470	55 (35–80)	43	94	8	9.5

* All studies were open label and all were parallel design except for that by Garg and colleagues (25), which was a crossover design. All studies were multicenter trials conducted in the United States and Canada except for that by Barnett and colleagues (24) and Exubera study 1002 (9), which were conducted in multiple countries, and Hermansen and colleagues (18), which was conducted in northern Europe. Heise and colleagues (12) did not report study site. The inhaled insulin device used in all trials was Exubera (Pfizer Inc., New York, New York), except for the study by Garg and colleagues (25), which used a breath-actuated delivery device (AIR particle technology, Alkermes, Inc., Cambridge, Massachusetts, and Eli Lilly, Inc., Indianapolis, Indiana), and the study by Hermansen and colleagues (18), which used an insulin liquid formulation (AERx Insulin Diabetes Management System, Novo Nordisk, Inc., Princeton, New Jersey). ASP = insulin aspart; BID = twice a day before breakfast and either before supper or bedtime; GLA = insulin glargine; GLIB = glibenclamide; LIS = insulin lispro; MET = metformin; NPH = neutral protamine Hagedorn insulin; NR = not reported; OHA = oral hypoglycemic agents (individual agents not specified); REG = regular insulin; ROS = rosiglitazone 4 mg BID; SU = sulfonylurea (glyburide or glipizide); TID = three times per day; TZD = thiazolidinedione; UL = ultralente insulin.
† Only adult patients (>18 years) were included in the meta-analyses.
‡ The baseline hemoglobin A_{1c} level in the 2 groups was statistically different: 8.7% in the inhaled insulin group versus 7.9% in the subcutaneous insulin group.
§ Hermansen and colleagues (18) reported a mostly Scandinavian sample presumed to be primarily white.
‖ Rosenstock and colleagues' study (22) involved 2 treatment groups (study A [inhaled insulin TID with meals alone, $n = 102$] and study B [inhaled insulin TID with meals added to MET/TZD and SU, $n = 100$]) versus 1 control group (MET/TZD and SU, $n = 96$).

ratio, 1.15 [CI, 0.96 to 1.38]; 27.1% with inhaled insulin vs. 24.6% with subcutaneous insulin).

Inhaled Insulin versus Oral Hypoglycemic Agents

When we combined data from studies that compared inhaled insulin with oral hypoglycemic agents in patients with type 2 diabetes, inhaled insulin lowered hemoglobin A_{1c} levels compared with oral agents (weighted mean difference, −1.04% [CI, −1.59% to − 0.49%]) (**Figure 2**) but with some heterogeneity among the trials. Three studies with 4 treatment groups (17, 21, 22) showed a large difference in hemoglobin A_{1c} levels favoring inhaled insulin (weighted mean difference, −1.45% [CI, −1.80% to −1.10%]), whereas 2 studies (9, 24) showed only a small difference favoring inhaled insulin (weighted mean difference, −0.20% [CI, −0.34% to − 0.07%]) (**Figure 2**). The latter 2 trials differed from the former 3 trials by including more participants, by having a longer duration (24 vs. 12 weeks, respectively), and by titrating the dose of therapy in both groups (inhaled insulin vs. oral hypoglycemic agents) to achieve glycemic targets.

Patients with type 2 diabetes who were taking inhaled insulin were more likely to achieve hemoglobin A_{1c} levels less than 7% than were those taking oral agents (risk ratio, 1.87% [CI, 1.07% to 3.25%]; 30.9% vs. 16.9%, respectively).

Non–Glucose-Related Outcomes

Eleven trials (9, 15–17, 19–25) reported limited data on changes in weight. In patients with type 1 or type 2

Table—Continued

Treatment Group		Control Group		Study Quality			
Inhaled Insulin	Subcutaneous Basal Insulin	Subcutaneous Meal Insulin	Subcutaneous Basal Insulin	Efficacy vs. Safety/Noninferiority vs. Superiority	Method of Randomization Described	Intention-to-Treat	Dropout Rate, %
TID with meals	UL at bedtime	REG BID	NPH BID	Efficacy/noninferiority	Yes	Yes	3
TID with meals	UL at bedtime	REG BID	NPH BID	Efficacy/noninferiority	No	No	11
TID with meals	NPH BID	REG TID with meals	NPH BID	Efficacy/noninferiority	No	No	7
TID with meals	NPH BID	REG TID with meals	NPH BID	Safety/NR	Yes	No	11
TID with meals	NPH/UL BID or GLA at bedtime	REG/LIS/ASP TID with meals	NPH/UL BID or GLA at bedtime	Safety/NR	No	NR	22
TID with meals	NPH/UL BID or GLA at bedtime	REG/LIS TID with meals	NPH/UL BID or GLA at bedtime	Safety/NR	No	NR	13
TID with meals	GLA at bedtime	REG/LIS TID with meals	GLA at bedtime	Efficacy/noninferiority	No	Yes	13
TID with meals	UL at bedtime	REG BID	NPH BID	Efficacy/noninferiority	No	No	9
TID with meals	NPH at bedtime	REG BID	NPH BID	Efficacy/superiority	No	Yes	10
TID with meals	UL at bedtime	REG BID	NPH BID	Efficacy/ noninferiority	Yes	No	9
TID with meals	NPH/UL BID or GLA at bedtime	REG/LIS/ASP TID with meals	NPH/UL BID or GLA at bedtime	Safety/NR	No	NR	25
Inhaled Insulin	**Oral Agents**	**Oral Agents**					
TID with meals	1–2 OHA	1–2 OHA		Efficacy/superiority	Yes	Yes	0
TID with meals	None	MET/TZD and SU		Efficacy/superiority	Yes	Yes	6
TID with meals	MET/TZD and SU	MET/TZD and SU					
TID with meals	None	ROS		Efficacy/superiority	Yes	Yes	6
TID with meals	SU	SU and MET		Efficacy/superiority	Yes	Yes	9
TID with meals	MET	MET and GLIB		Efficacy/superiority	Yes	NR	10

diabetes, there was no difference in weight gain (range, 0.2 to 1.5 kg) in the inhaled insulin and subcutaneous insulin groups except in 1 study (19), which reported a 1.3-kg weight loss in the inhaled insulin group compared with the subcutaneous insulin group in those with type 2 diabetes. Inhaled insulin resulted in more weight gain than combination oral therapy (adjusted mean difference, 1.85 kg [CI, 0.98 kg to 2.73 kg]) (17, 22, 24), but there was no difference compared with rosiglitazone monotherapy (adjusted mean difference, 0.95 kg [CI, −0.18 kg to 2.09 kg]) (21).

Safety

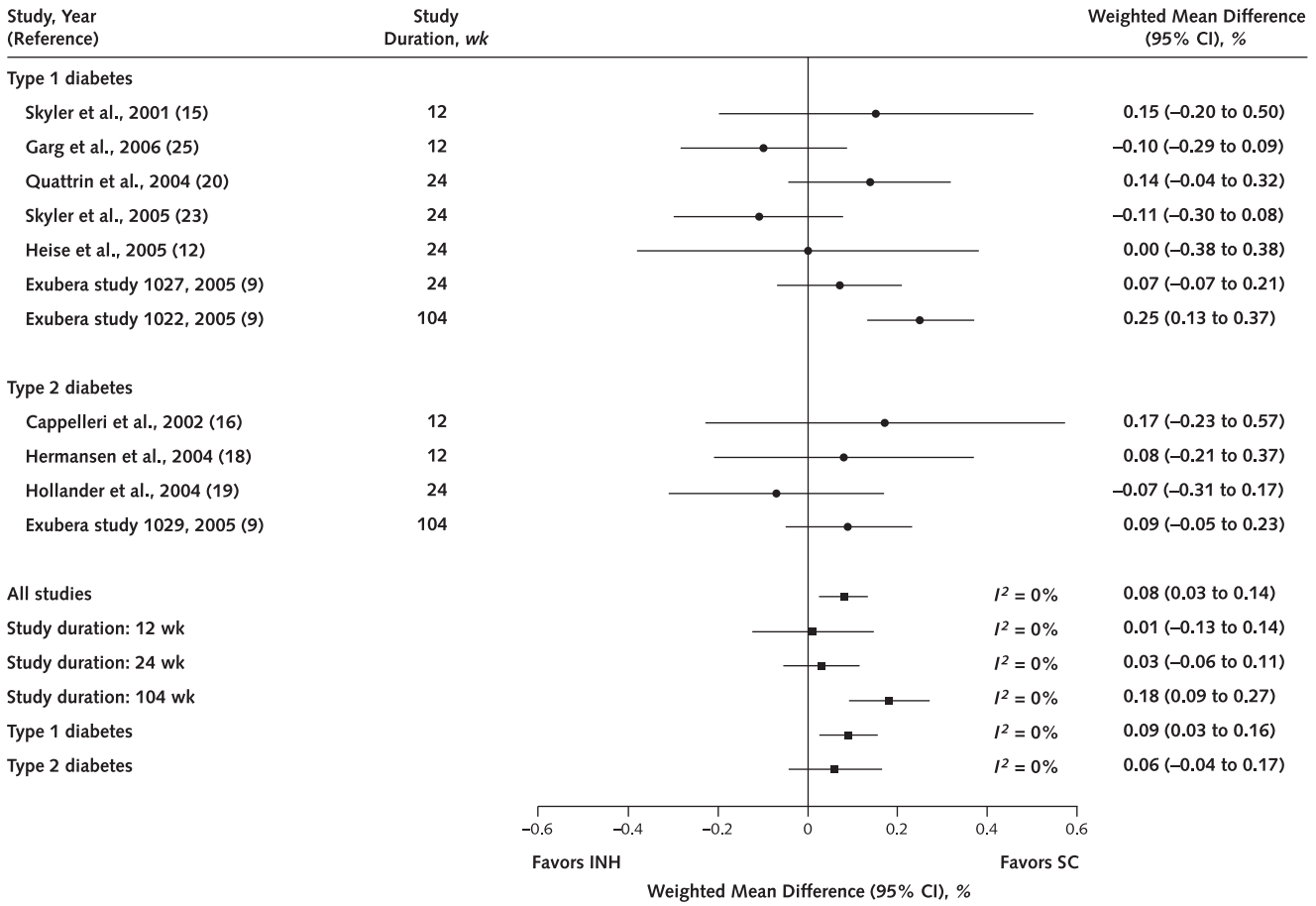
Severe Hypoglycemia

There was no difference between inhaled insulin and subcutaneous insulin in the proportion of patients reporting at least 1 episode of severe hypoglycemia (risk ratio, 1.00 [CI, 0.95 to 1.04]). There was no difference in the risk ratio between inhaled insulin and subcutaneous insulin among patients with type 1 or type 2 diabetes; however, severe hypoglycemia was reported in a higher proportion of patients with type 1 diabetes (75% in the inhaled insulin group vs. 78% in the subcutaneous insulin group) than in those with type 2 diabetes (16% vs. 18%, respectively). A higher proportion of patients treated with inhaled insulin reported at least 1 episode of severe hypoglycemia compared with those taking oral agents (risk ratio, 3.06 [CI, 1.03 to 9.07]; 9.4% vs. 3.5%, respectively).

Pulmonary Safety

All trials selected participants without a recent history of smoking (at least 6 months) or underlying pulmonary

Figure 1. **Weighted mean difference (error bars indicate 95% CIs) in change in hemoglobin A_{1c} level for inhaled (*INH*) versus subcutaneous (*SC*) insulin in adults with type 1 or type 2 diabetes.**



The I^2 statistic describes the percentage of total variation across studies, which is due to heterogeneity rather than chance (14).

disease, such as asthma, interstitial lung disease, or chronic obstructive pulmonary disease. All participants had a normal chest radiograph and pulmonary function test results at baseline. Pulmonary safety was assessed by self-reporting of respiratory symptoms and by pulmonary function tests.

The most common pulmonary symptom associated with inhaled insulin was a nonproductive cough, which was reported more frequently in patients taking inhaled insulin than in those in the comparison group receiving subcutaneous insulin or oral agents (risk ratio, 3.52 [CI, 2.23 to 5.56]; 16.9% vs. 5.0%, respectively). There were no differences between patients with type 1 or type 2 diabetes. Cough occurred within seconds to minutes after administration of inhaled insulin; it was mild and was not associated with changes in pulmonary function. Cough was noted early in the treatment course (within the first month) and diminished in frequency and severity over time.

Patients receiving inhaled insulin had a greater decrease in FEV_1 from baseline than did those in the comparison group (weighted mean difference, −0.031 L [CI, −0.043 L to − 0.020 L]) (**Figure 3**). The small decrease in FEV_1 seen with inhaled insulin was statistically significant compared with subcutaneous insulin in patients with type 1 diabetes and compared with oral hypoglycemic agents in patients with type 2 diabetes (**Figure 3**). The decrease in FEV_1 was slowly progressive over the first 6 months but stabilized in studies of up to 2 years' duration (9).

Among patients with type 1 diabetes, inhaled insulin was associated with a greater decrease in DL_{CO} from baseline than was subcutaneous insulin (weighted mean difference, −0.902 mL/min per mm Hg [CI, −1.546 to − 0.258 mL/min per mm Hg]) (**Figure 4**). The decrease in DL_{CO} was evident in studies with durations of 24 weeks or less (9, 12, 15, 20, 23, 25), although there was no difference in the 2-year study (9). In a 12-week crossover trial, DL_{CO} returned toward baseline levels after patients were switched to subcutaneous insulin (25). Among patients with type 2 diabetes, there was no difference in DL_{CO} from baseline between the inhaled insulin group and the comparison group in studies up to 2 years in duration (9) (**Figure 4**).

When data were combined from all inhaled insulin trials, 2% of patients with type 1 diabetes and 2.3% of patients with type 2 diabetes receiving inhaled insulin discontinued treatment because of respiratory events, versus 0% and 0.1%, respectively, in the comparison group (subcutaneous insulin or oral hypoglycemic agents).

Insulin Antibodies

Higher levels of insulin antibodies were seen after administration of inhaled insulin versus subcutaneous insulin, especially among patients with type 1 diabetes, in the 7 trials that reported such data (12, 18–20, 22, 23, 25). However, the level of insulin antibodies was not associated with any measured clinical outcomes, including dosing requirements for inhaled insulin, glycemic control, or adverse outcomes (allergic events, pulmonary side effects, or hypoglycemia).

Patient-Reported Outcomes

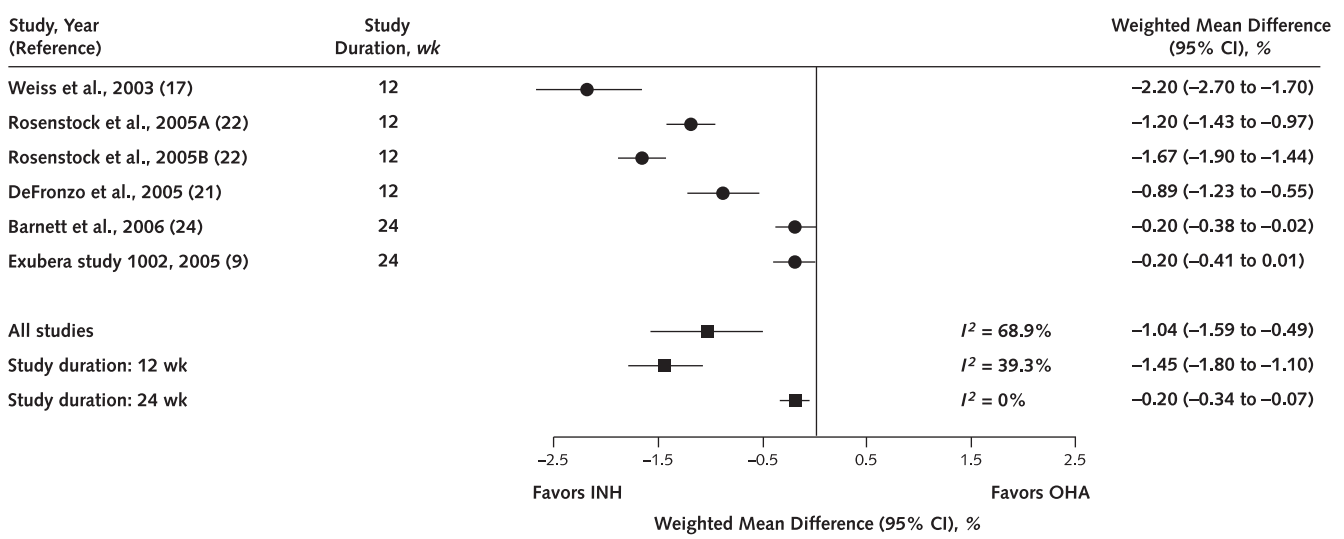
Four trials in patients with type 1 (15, 20) or type 2 (16, 19) diabetes reported data on overall patient satisfaction for inhaled insulin versus subcutaneous insulin. All trials reported a statistically significant increase in overall patient satisfaction with inhaled insulin over subcutaneous insulin. Areas of improvement included ease of administration, comfort, convenience, mealtime flexibility, and ease of taking insulin many times a day. Two studies reported statistically significant improvements in overall quality of life with inhaled insulin (19, 20). Patients randomly assigned to inhaled insulin were more likely to continue taking inhaled insulin than to switch back to subcutaneous insulin (15, 16).

Discussion

Advances in medical technology have frequently improved patient care, but the introduction of a new technology also poses certain challenges. Most health care providers and patients place a high value on new technology and quickly embrace it; however, there is considerable controversy regarding which devices to use, when to use them, and what value they bring to health care (26). As with new medications, an evidence-based assessment of the new technology should be performed with emphasis not only on efficacy and safety from randomized, controlled trials but also on patient preferences, including how the new technology can enhance quality of life. Our analysis of randomized, controlled trials designed for efficacy or safety showed that inhaled insulin is comparable to subcutaneous regular insulin in lowering glycemia in adults with type 1 or type 2 diabetes. Compared with oral hypoglycemic agents, inhaled insulin yielded a greater reduction in glycemia than did fixed doses of oral agents in patients with type 2 diabetes. Inhaled insulin was associated with dry cough and a mild nonprogressive decrease in pulmonary function and was preferred by patients over subcutaneous insulin.

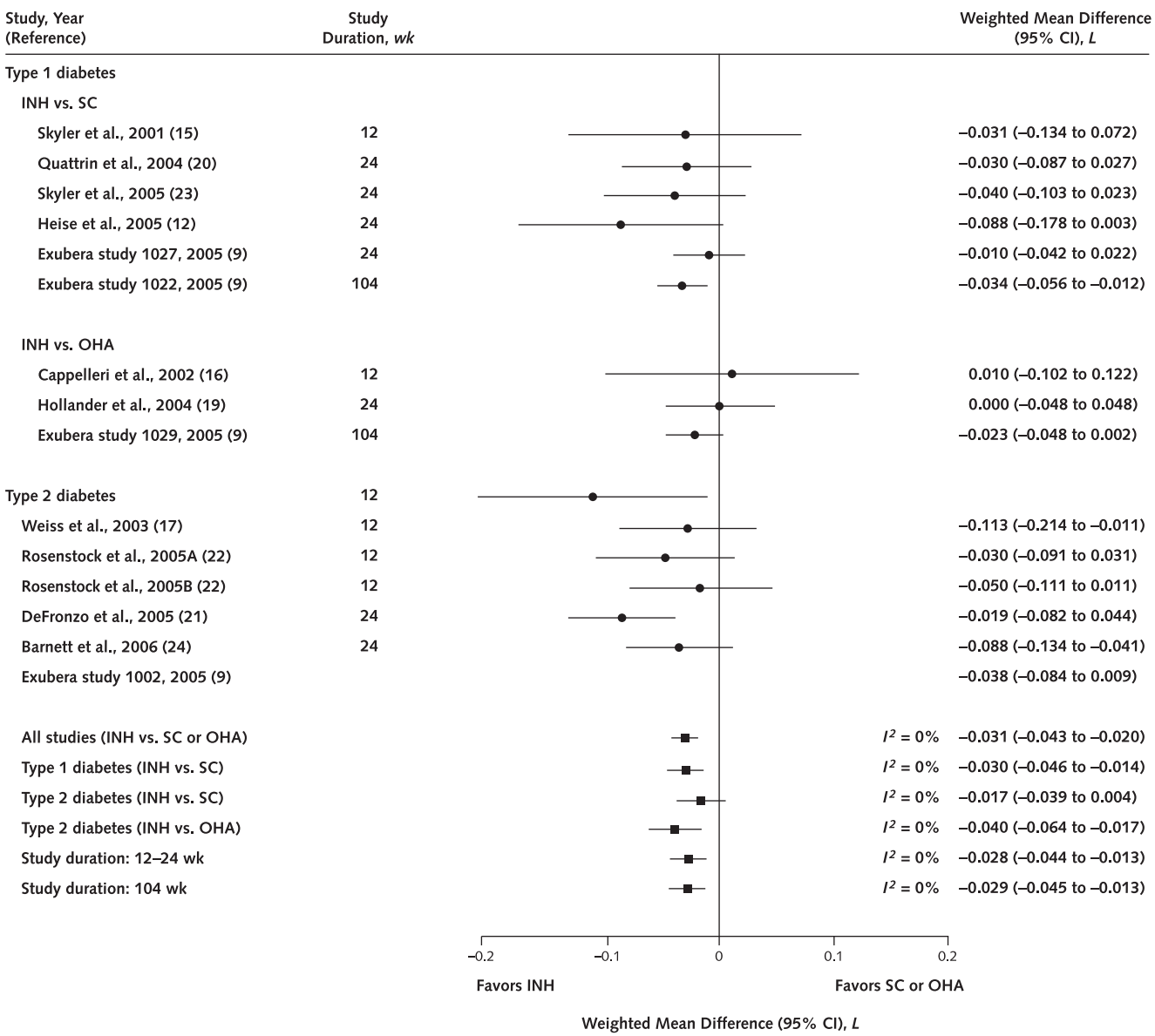
The comparable glycemic efficacy between inhaled insulin and subcutaneous insulin was consistent among the reviewed studies. There was no heterogeneity among patients with type 1 or type 2 diabetes. There was also no difference between the proportion of patients receiving inhaled insulin or subcutaneous insulin who achieved the hemoglobin A_{1c} target of less than 7% (27% vs. 24%, respectively); however, these proportions are much lower

Figure 2. **Weighted mean difference (error bars indicate 95% CIs) in change in hemoglobin A_{1c} level for inhaled (*INH*) versus oral hypoglycemic agents (*OHAs*) in adults with type 2 diabetes.**



The I^2 statistic describes the percentage of total variation across studies that is due to heterogeneity rather than chance (14). Rosenstock and colleagues (22) had 2 intervention groups (study A [inhaled insulin alone] and study B [inhaled insulin added to oral hypoglycemic agents]) versus 1 control group (oral hypoglycemic agents).

Figure 3. **Weighted mean difference (error bars indicate 95% CIs) in change in FEV_1 in liters for inhaled insulin (*INH*) versus control (subcutaneous insulin [*SC*] or oral hypoglycemic agents [*OHAs*]) in adults with type 1 or type 2 diabetes.**



The I^2 statistic describes the percentage of total variation across studies that is due to heterogeneity rather than chance (14). Rosenstock and colleagues (22) had 2 intervention groups (study A [inhaled insulin alone] and study B [inhaled insulin added to oral hypoglycemic agents]) versus 1 control group (oral hypoglycemic agents).

compared with those achieved with intensive subcutaneous insulin therapy in the Diabetes Control and Complications Trial (27) or in the U.K. Prospective Diabetes Study (28), which were both published more than a decade earlier. The decreased efficacy compared with older trials may be due to the noninferiority design of the inhaled insulin trials; however, without having shown the superiority of inhaled insulin, it is important to avoid having patients replace their current subcutaneous insulin therapy with inhaled insulin and expect the same degree of glycemic control.

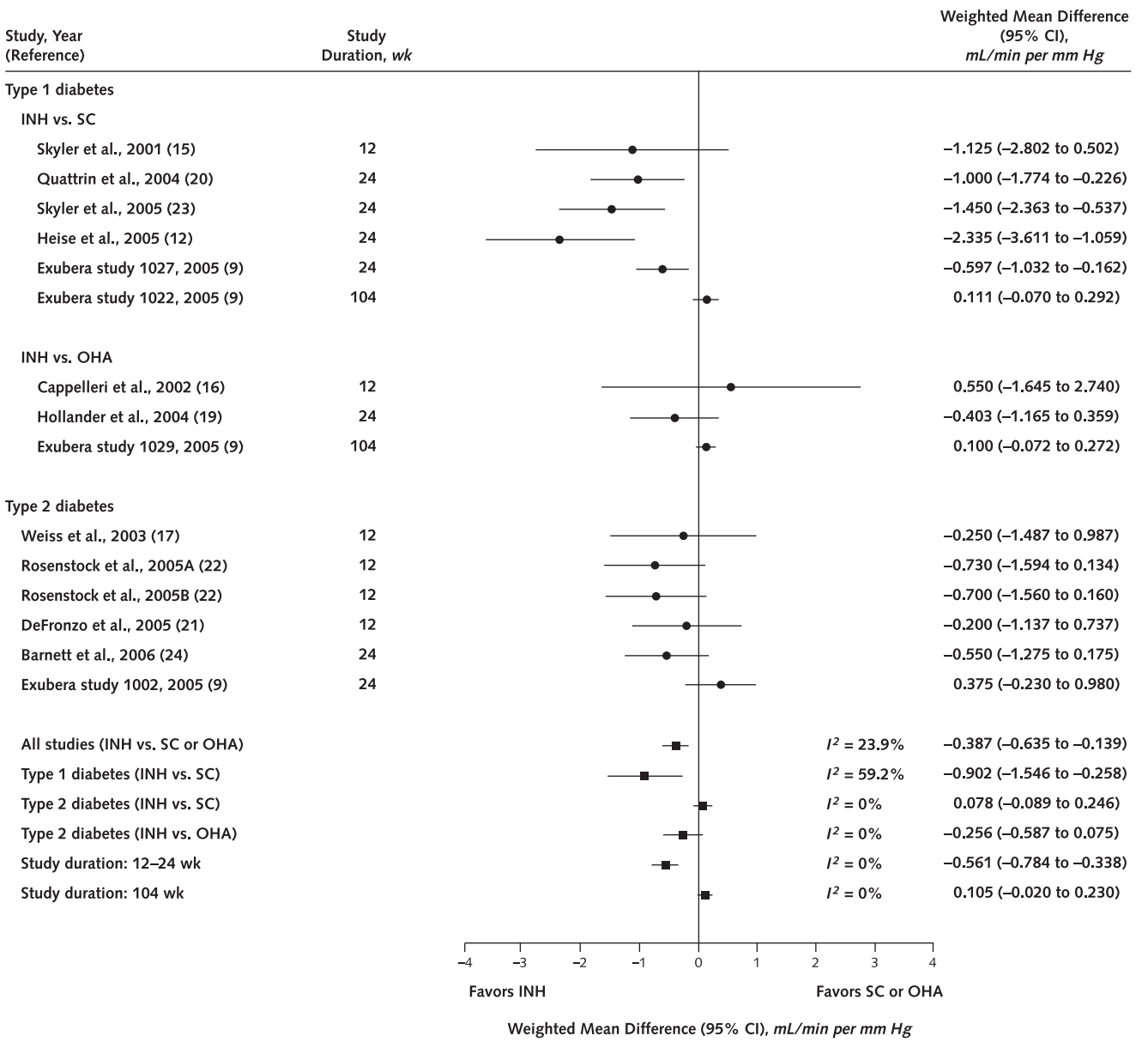
It is difficult to directly compare the efficacy of inhaled insulin versus individual oral agents because most studies comparing these therapies were heterogeneous in relation to baseline hemoglobin A_{1c} levels and the type of oral agents used. Yet, the finding that inhaled insulin improves glycemia more than fixed doses of oral agents is consistent with previous observations that have reported a higher efficacy of insulin versus oral therapy in achieving long-term glycemic targets (28). Of note, however, the superior glycemic outcome of inhaled insulin was seen in short (12-week) trials that titrated inhaled insulin to a glucose target but did not titrate oral medication doses. In the two 24-

week studies (9, 24), in which the dose of the oral agents was titrated to glucose goals, there was only a small difference between inhaled and oral agents in glycemic efficacy even though the studies were designed to show the superiority of inhaled insulin.

The 3-fold increased risk for severe hypoglycemia for patients in the inhaled insulin group compared with those receiving oral agents is not surprising because of improved glycemic control and previous observations with subcutaneous insulin therapy (29). The rate of severe hypoglycemia in clinical practice is difficult to predict and may be initially high because of the novelty of using a new delivery device, but the risk should diminish with more training and practice. Furthermore, dose adjustments with available inhaled insulin devices have yet to be perfected for the finer small-increment dosing needed to avoid hypoglycemia, especially in insulin-sensitive patients.

A major concern with inhaled insulin is the potential

Figure 4. **Weighted mean difference (error bars indicate 95% CIs) in change in diffusing capacity of carbon monoxide (DL_{CO} in mL/min per mm Hg) for inhaled insulin (*INH*) versus control (subcutaneous insulin [*SC*] or oral hypoglycemic agents [*OHAs*]) in adults with type 1 or type 2 diabetes.**



The I^2 statistic describes the percentage of total variation across studies that is due to heterogeneity rather than chance (14). Rosenstock and colleagues (22) had 2 intervention groups (study A [inhaled insulin alone] and study B [inhaled insulin added to oral hypoglycemic agents]) versus 1 control group (oral hypoglycemic agents).

for pulmonary toxicity because of the immunogenic and growth-promoting properties of insulin. Because of its timing immediately after inhalation, the mild to moderate cough seen with inhaled insulin seems to be directly related to the delivery method, including potential irritation from excipients. Small decreases in FEV_1 and DL_{CO} occurred early in the treatment and did not progress over 2 years. Because patients with diabetes have reduced baseline pulmonary function and more rapid decreases in pulmonary function over time compared with healthy controls (30–33), small decreases in FEV_1 and DL_{CO} induced by inhaled insulin may have potential clinical significance. Although there were no clinically significant pulmonary sequelae during the 2-year safety trials, the potential for pulmonary toxicity with long-term administration of inhaled insulin is of concern, and studies of longer duration (>2 years) and careful postmarketing surveillance in clinical practice are needed to fully evaluate the effects of inhaled insulin on lung function.

All trials excluded patients with a recent history of tobacco use because smoking increases the rate of absorption and the bioavailability of inhaled insulin in healthy volunteers (34), and changes in smoking habits greatly and rapidly alter the pharmacokinetics of inhaled insulin (35). Because of unpredictable absorption with changes in smoking behavior, inhaled insulin is contraindicated in patients who smoke, including those who have quit smoking recently. Patients who smoke may represent up to a quarter of the diabetes population in the United States (36).

All trials included patients with normal baseline lung function, and there are only limited data for patients with asthma and chronic obstructive pulmonary disease (9). After a single dose of inhaled insulin, nondiabetic patients with asthma absorbed less insulin than did healthy participants, resulting in less glucose reduction without a change in airway reactivity (37). However, nondiabetic former smokers with chronic obstructive pulmonary disease absorbed more insulin than did controls (9). Efficacy and safety studies are ongoing in insulin-requiring patients with diabetes and asthma or chronic obstructive pulmonary disease (9). Finally, the pharmacokinetics of inhaled insulin did not differ during the acute or recovery phase of an upper respiratory infection in patients without diabetes (38), but there are no data on the pharmacokinetics of inhaled insulin during infections of the lower respiratory tract. Because patients with diabetes are at greater risk for chronic lung conditions and acute respiratory infections (39), a better characterization of the efficacy and safety of inhaled insulin is warranted in patients with diabetes and pulmonary disease.

Patients with diabetes were more satisfied with inhaled insulin and preferred it to subcutaneous insulin. In 1 study in which patients received educational information, the availability of inhaled insulin as a treatment option substantially increased the proportion of patients who would theoretically choose insulin overall (40). Furthermore, patients with poorly controlled type 2 diabetes were more likely to choose and accept insulin therapy if inhaled insulin was offered (40). The enhanced willingness to embrace inhaled insulin increases the potential for improving glycemic control in the diabetes population. However, increased patient acceptability of inhaled insulin may be related to the novelty of the new delivery method, and it remains to be seen whether patients will prefer and adhere to the new delivery method in clinical practice. Of importance, adherence also depends on the characteristics of the delivery device and cost that will become evident in the clinical setting.

Our review has limitations related to the included studies. First, all trials were open label and none used inhaler or injection placebos ("double-dummy" technique). Historically, insulin trials have not been double-blind because of logistic, ethical, and safety concerns. In the case of inhaled insulin, the use of a "double-dummy" technique would have added to the complexity of conducting the trials. Nevertheless, open-label trials have the potential for bias in conducting the intervention and ascertaining subjective outcomes, such as cough and patient preference. Next, because most patients were white, differential effects of inhaled insulin by race or ethnicity could not be assessed in these trials. In addition, only 2 trials were long term (2 years) (9), thus limiting assessment of long-term safety. Finally, we included data from unpublished studies found only in the FDA briefing documents. Although these studies have not undergone traditional peer review, we considered FDA review equivalent to peer review.

In conclusion, inhaled insulin offers an alternative noninvasive option for premeal insulin administration with glycemic efficacy comparable to subcutaneous regular insulin and increased patient acceptability. Because of concerns for long-term pulmonary toxicity; unpredictable variability in patients with acute respiratory conditions; the lack of cost-effectiveness studies; and the availability of an effective, safe, and familiar alternative in subcutaneous insulin, inhaled insulin should be reserved for patients without pulmonary conditions who are needle-phobic and would otherwise experience delays in appropriate and timely therapy with insulin. This new insulin technology will need continued evaluation in long-term efficacy and safety trials and in clinical practice to measure its effectiveness and to determine its place in the armamentarium of diabetes therapies.

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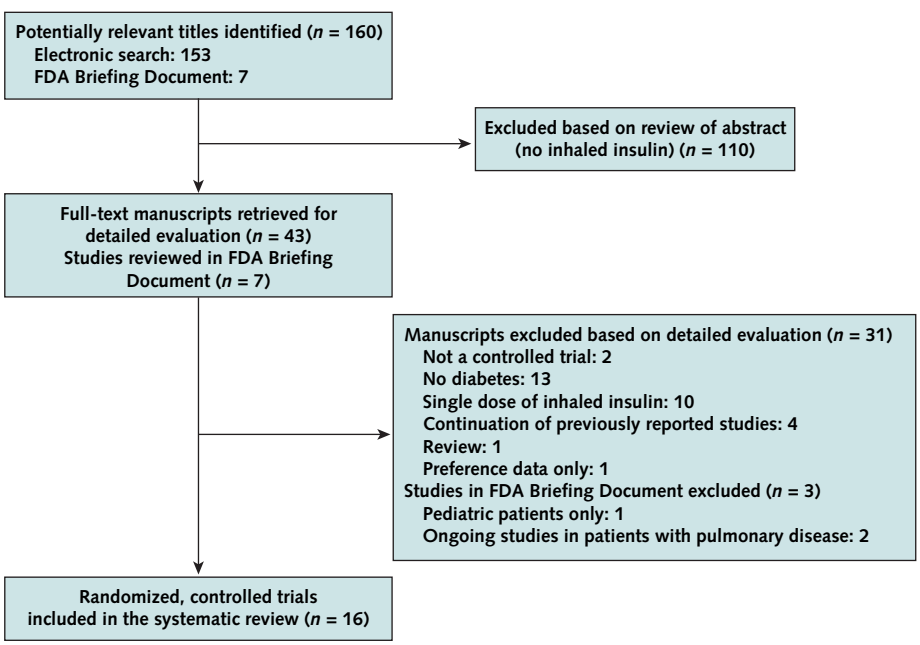
Appendix Figure. **Search results.**



FDA = U.S. Food and Drug Administration.