Quantifying the Effect of Metformin Treatment and Dose on Glycemic Control

Jennifer A. Hirst, msc[1]
Andrew J. Farmer, md[1]
Raghib Ali, msc[2,3]
Nia W. Roberts, msc[4]
Richard J. Stevens, phd[1]

OBJECTIVE—Metformin is the first-line oral medication recommended for glycemic control in patients with type 2 diabetes. We reviewed the literature to quantify the effect of metformin treatment on glycated hemoglobin (HbA_{1c}) levels in all types of diabetes and examine the impact of differing doses on glycemic control.

RESEARCH DESIGN AND METHODS—MEDLINE, EMBASE, and the Cochrane Library were searched from 1950 to June 2010 for trials of at least 12 weeks' duration in which diabetic patients were treated with either metformin monotherapy or as an add-on therapy. Data on change in HbA_{1c} were pooled in a meta-analysis. Data from dose-comparison trials were separately pooled.

RESULTS—A total of 35 trials were identified for the main analysis and 7 for the dose-comparison analysis. Metformin monotherapy lowered HbA_{1c} by 1.12% (95% CI 0.92–1.32; $I^2 = 80\%$) versus placebo, metformin added to oral therapy lowered HbA_{1c} by 0.95% (0.77–1.13; $I^2 = 77\%$) versus placebo added to oral therapy, and metformin added to insulin therapy lowered HbA_{1c} by 0.60% (0.30–0.91; $I^2 = 79.8\%$) versus insulin only. There was a significantly greater reduction in HbA_{1c} using higher doses of metformin compared with lower doses of metformin with no significant increase in side effects.

CONCLUSIONS—Evidence supports the effectiveness of metformin therapy in a clinically important lowering of HbA_{1c} used as monotherapy and in combination with other therapeutic agents. There is potential for using higher doses of metformin to maximize glycemic control in diabetic patients without increasing gastrointestinal effects.

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Metformin is the most commonly prescribed antihyperglycemic medication for diabetes in the U.S. (1) and the U.K. (2) and is the recommended first choice for oral therapy (2–4). The role of metformin in glucose lowering has been associated with a reduction in cardiovascular outcomes (5,6). However, its effectiveness in glycemic control is not well documented, although estimates based on trials suggest that it reduces glycated hemoglobin (HbA_{1c}) by 1–2% (11–22 mmol/mol) (3,7). A recent systematic review (8) suggested that this is an overestimate of effect, but the meta-analysis included only seven trials of metformin, and it did not separately examine metformin use as a monotherapy or in combination with other antihyperglycemic medications. We therefore conducted a systematic review and meta-analysis of randomized controlled trials of metformin with the aim of *1*) quantifying its reduction in HbA_{1c}, *2*) exploring the different treatment effects when administered as a monotherapy or as an add-on therapy, and *3*) examining head-to-head trials of low versus high metformin doses to understand the effect metformin dose has on HbA_{1c} reduction.

RESEARCH DESIGN AND METHODS

Search strategy and study selection

MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials were searched from 1950 to June 2010. Abstracts of identified articles were reviewed by two reviewers, and full texts were examined by two reviewers (J.A.H. and R.A.). For inclusion, trials were required to fulfill the following criteria: *1*) be a randomized controlled design; *2*) report data on participants with diabetes; *3*) have a patient follow-up of at least 12 weeks; *4*) have a treatment group of metformin monotherapy, or metformin as an add-on therapy; *5*) have a placebo or background treatment comparator group; *6*) randomize patients to a fixed dose of metformin; *7*) blind patients to oral medications; *8*) use the same metformin dose for each patient in the trial; and *9*) use the same fixed dose of any other oral glucose-lowering medication used in combination with metformin in both the metformin and comparator arms.

Data extraction and quality assessment

Data were abstracted using standardized forms to include trial characteristics (design and duration), interventions, trial quality, patient characteristics, and outcome measures. The quality of trials was assessed using items for selection bias, treatments, outcome measurement statistical methods, and outcome assessment. Outcome measures were the change in HbA_{1c} levels from baseline to the end of the trial, total adverse events, and gastric adverse events (diarrhea and abdominal cramps). In 12 trials where change in HbA_{1c} was not reported, it was calculated from baseline and end point data, and SD of the change was estimated from baseline and end point SDs (9). In five trials, SD of HbA_{1c} was not given, and it was imputed by averaging the SDs from trials in which it was reported (9). Trials in which data were estimated or imputed were excluded from the meta-analysis in a sensitivity analysis. When a study had two metformin arms of

From the [1]Department of Primary Care Health Sciences, University of Oxford, Oxford, U.K., and the National Institute for Health Research School for Primary Care Research, Oxford, U.K.; the [2]Cancer Epidemiology Unit, University of Oxford, Oxford, U.K.; the [3]Department of Community Medicine, United Arab Emirates University, Al Ain, United Arab Emirates; and the [4]Bodleian Health Care Libraries, University of Oxford, Oxford, U.K.
Corresponding author: Jennifer A. Hirst, jennifer.hirst@phc.ox.ac.uk.
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Table 1—*Included studies*

Trial	*n*	Intervention	Metformin dose (mg)	Comparator	Age (years)	BMI	Duration of diabetes (years)	Primary outcome	Length of trial (weeks)	Type of diabetes
Monotherapy trials										
Fujioka 2005	379	Metformin	500, 2,000	Placebo	54.7	30.5	2.9	Change in HbA_{1c}	16	2
Garber 1997	229	Metformin	500, 2,500	Placebo	57	32	—	Change in FPG	14	2
Horton 2000	350	Metformin	500	Placebo	58.2	29.4	4.5	Change in HbA_{1c}	24	2
Goldstein 2007	520	Metformin	1,000	Placebo	53.4	32.3	4.5	Change in HbA_{1c}	24	2
Hallsten 2002	27	Metformin	1,000	Placebo	57.7	30	—	Insulin responsiveness in skeletal muscle	26	2
Viljanen 2005	23	Metformin	1,000	Placebo	58.2	29.7	—	Adipose tissue glucose uptake	26	2
Iozzo 2003	21	Metformin	1,000	Placebo	58	29.8	1–3	Hepatic glucose uptake	26	2
Chiasson 2001	163	Metformin	1,500	Placebo	57.8	30.9	6.3	Change in HbA_{1c}	30	2
Natali 2004	50	Metformin	1,500	Placebo	58	29	5.0	Vascular reactivity	16	2
List 2009	110	Metformin	1,500	Placebo	53.5	32	—	Change in HbA_{1c}	12	2
Grant 1996	75	Metformin	1,500, 3,000	Placebo	—	—	—	Glycemic control	26	2
Wolever 2000	107	Metformin	1,500	Placebo	58.6	30.6	6.1	Serum folate levels	36	2
Hoffmann 1997	63	Metformin	1,700	Placebo	58.1	26.9	2.9	Change in HbA_{1c}	24	2
DeFronzo 1995	289	Metformin	2,500	Placebo	53	29.5	6	Diabetes control	24	2
Damsbo 1998	18	Metformin	3,000	Placebo	52	32	Newly diagnosed	Glycogen synthase activity	12	2
Combination trials										
Jadzinsky 2009	658	Metformin + saxagliptin	500	Saxagliptin	52.1	30.2	1.6	Change in HbA_{1c}	24	2
Perez 2009	390	Metformin + pioglitazone	850	Pioglitazone	54.4	31	—	Change in HbA_{1c}	24	2
Bosi 2009	885	Metformin + vildagliptin	1,000, 2,000	Vildagliptin	52.9	31.2	2.0	Change in HbA_{1c}	24	2
Lewin 2007	434	Metformin + sulfonylurea	1,500, 2,000	Sulfonylurea	53.3	34.5	5.3	Change in HbA_{1c}	24	2
Wolever 2000	92	Metformin + miglitol	1,500	Miglitol	58.2	30.3	5.0	Serum folate levels	36	2
Chiasson 2001	155	Metformin + miglitol	1,500	Miglitol	58.1	30.3	5.6	Change in HbA_{1c}	30	2
Horton 2000	351	Metformin + nateglinide	1,500	Nateglinide	58.5	29.3	4.6	Change in HbA_{1c}	24	2
Moses 1999	55	Metformin + repaglinide	1,750	Repaglinide	58.8	32.2	6.5	Change in HbA_{1c}	12	2
DeFronzo 1995	422	Metformin + glyburide	2,500	Glyburide	55.5	29	8.2	Diabetes control	24	2

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Table 1—*Continued*

Trial	*n*	Intervention	Metformin dose (mg)	Comparator	Age (years)	BMI	Duration of diabetes (years)	Primary outcome	Length of trial (weeks)	Type of diabetes
Derosa 2009	127	Metformin + pioglitazone	2,550	Pioglitazone	55.5	27.5	—	Insulin sensitivity	64	2
Goldstein 2007	536	Metformin + sitagliptin	1,000, 2,000	Sitagliptin	53.6	31.8	4.4	Change in HbA_{1c}	24	2
Williams-Herman 2009	406	Metformin + sitagliptin	1,000, 2,000	Sitagliptin	53.6	31.6	4.2	Change in HbA_{1c}	54	2
Insulin trials										
Robinson 1998	38	Metformin + insulin	1,000	Placebo + insulin	61.3	30.1	15	Glycemic control	12	2
Giugliano 1993	50	Metformin + fixed-dose insulin	1,700	Placebo + fixed-dose insulin	60.4	32.9	11.6	Glycemic control	26	2
Hermann 2001	35	Metformin + fixed-dose insulin	1,700	Placebo + fixed-dose insulin	57.6	33.1	13	Glycemic control	52	2
Meyer 2002	62	Metformin + insulin	1,700	Placebo + insulin	40.0	26.1	19.3	Blood glucose control	26	1
Ponssen 2000	31	Metformin + insulin	1,700	Placebo + insulin	61.8	28	10	Dose of insulin required for glycemic control	20	2
Douek 2005	175	Metformin + insulin	2,000	Placebo + insulin	58	31.2	9.5	Weight gain	52	2
Jacobsen 2009	24	Metformin + insulin	2,000	Placebo + insulin	40.4	29.4	19.1	Glycemic control	24	1
Lund 2008	98	Metformin + insulin	2,000	Placebo + insulin	45.5	26	28	Change in HbA_{1c}	52	1
Ryysy 2001	41	Metformin + sulfonylurea + insulin	2,000	Placebo + sulfonylurea + insulin	58.4	28.7	>3	Glycemic control	52	2
Yki-Järvinen 1999	45	Metformin + glyburide + insulin	2,000	Placebo + glyburide + insulin	57.9	29.6	>3	Weight gain	52	2
Wulffelé 2002	353	Metformin + insulin	2,163	Placebo + insulin	61.0	29.7	13	Cardiovascular morbidity	16	2
Aviles Santa 1999	43	Metformin + insulin	2,500	Placebo + insulin	53.9	—	9.7	Glycemic control	16	2
Khan 2006	30	Metformin + insulin	2,550	Placebo + insulin	48	31.3	19	Blood glucose control	16	1
Dose-comparison trials										
Garber 1997	299	Metformin (2,257 mg)		Metformin (1,255 mg)	58.3		—	Change in FPG	14	2
Fujioka 2005	374	Metformin (2,000 mg)		Metformin (1,250 mg)	56		2.9	Change in HbA_{1c}	16	2
Goldstein 2007a	355	Metformin (2,000 mg)		Metformin (1,000 mg)	53.3		4.5	Change in HbA_{1c}	24	2
Goldstein 2007b	361	Metformin (2,000 mg) + sitagliptin		Metformin (1,000 mg) + sitagliptin	53.7		4.5	Change in HbA_{1c}	24	2
Williams-Herman 2009a	251	Metformin (2,000 mg)		Metformin (1,000 mg)	54.0		4.1	Change in HbA_{1c}	54	2

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Table 1—*Continued*

Trial	*n*	Intervention	Metformin dose (mg)	Comparator	Age (years)	BMI	Duration of diabetes (years)	Primary outcome	Length of trial (weeks)	Type of diabetes
Williams-Herman 2009b	300	Metformin (2,000 mg) + sitagliptin		Metformin (1,000 mg) + sitagliptin	53.7		4.4	Change in HbA_{1c}	54	2
Grant 1996	27	Metformin (3,000 mg)		Metformin (1,500 mg)	—		—	Glycemic control	24	2
Bosi 2009	585	Metformin (2,000 mg) + vildagliptin		Metformin (1,000 mg) + vildagliptin	52.7		1.9	Change in HbA_{1c}	24	2
Lewin 2007	290	Metformin (2,000 mg) + sulfonylurea		Metformin (1,500 mg) + sulfonylurea	53.5		5.1	Change in HbA_{1c}	24	2

References for all included trials are available in the Supplementary Data online. FPG, fasting plasma glucose. a, comparison of metformin monotherapy. b, comparison of metformin in combination with oral therapy.

different doses, we included both in the analysis and present results ordered by dose, splitting the comparator group into two to avoid covariance problems (9). When a study had more than two metformin arms, we selected the lowest and highest dose arms for inclusion in the analysis. Sensitivity analyses of trials of 24 weeks or longer were conducted to verify that the treatment effect observed was sustained in the longer trials.

A second review comparing head-to-head trials of two metformin doses was conducted. The same inclusion criteria were applied with the exception that the comparator arm included a different dose of metformin to the intervention arm. In each multiarm trial, we pooled arms with metformin doses of 1,000 and 1,500 mg into a single "low-dose" arm and arms with metformin dose >1,500 mg into a single "high-dose" arm for comparisons.

All of the trials covered in this review reported HbA_{1c} units as a percentage of total hemoglobin standardized to the methods of the Diabetes Control and Complications Trial (DCCT). Results are therefore reported in DCCT units as a percentage and have been converted into the new Standard International units using International Federation of Clinical Chemistry and Laboratory Medicine units of millimoles per mole of hemoglobin.

Statistical analysis

Data analysis was performed in Stata 11.1 (Stata Corporation, College Station, TX) using a random-effects model based on the DerSimonian and Laird method to pool the data, reporting the mean difference in change in HbA_{1c} levels between the metformin and comparator arms or high-dose versus low-dose metformin. Adverse-events data were analyzed using the Mantel-Haenszel method, with a random-effects model reporting risk ratio under the approximating assumption that adverse events occur independently. Heterogeneity was explored using subgroup analyses and metaregression to look at the effect of type of diabetes, trial size, BMI, age, metformin dose, baseline HbA_{1c} levels, length of follow-up, year of publication, country of trial, and change in HbA_{1c} in the comparator group.

RESULTS

Study characteristics

Searches identified 2,680 trials (Supplementary Fig. A1). These were screened on title and abstract to give 293 articles requiring examination of the full text. A total of 35 trials, representing 7,960 participants, met inclusion criteria (a full list of references of included trials is given in the Supplementary Data online). Of these, 15 were receiving metformin monotherapy compared with placebo, no treatment, or diet (2,424 participants); 12 were receiving metformin treatment in combination with another oral antihyperglycemic medication compared with the other medication (4,511 participants); and 13 were receiving metformin in combination with insulin treatment compared with patients on insulin treatment only (1,025 participants). Five trials with multiple arms (10–14) were included in the meta-analysis of both monotherapy and metformin combination. Seven trials were included in the dose-comparison analysis (2,842 participants). Details of the trial characteristics are shown in Table 1.

Quality of trials

All of the included trials were double blinded, with the exception of one trial from the insulin subgroup (15) in which the comparator group received an extra insulin injection and, thus, was only partially blinded. Of the 35 included trials, only 8 stated the method of randomization.

Metformin effectiveness

All monotherapy and combination oral therapy trials were conducted on patients with type 2 diabetes. In the metformin monotherapy trials, HbA_{1c} was reduced by 1.12% (95% CI 0.92–1.32; $P < 0.00001$, $I^2 = 80.2\%$), corresponding to a reduction of 12 mmol/mol more with metformin than placebo (Fig. 1). When we restricted the analysis to trials of ≥24 weeks, the HbA_{1c} in 10 trials was 1.19% lower (0.98–1.41; $I^2 = 71.2\%$) in the metformin groups versus placebo. In the trials of metformin as add-on to oral therapy, HbA_{1c} was reduced by 0.95% (0.77–1.13; $P < 0.00001$, $I^2 = 77.1\%$), corresponding to a reduction of 11 mmol/mol more with metformin than in the comparator group. When we restricted the analysis to trials of ≥24 weeks, the HbA_{1c} in 11 trials was 0.94% lower (0.76–1.13; $I^2 = 78.6\%$) in the metformin groups versus comparator groups.

In trials of metformin as add-on to insulin therapy, HbA_{1c} was reduced by

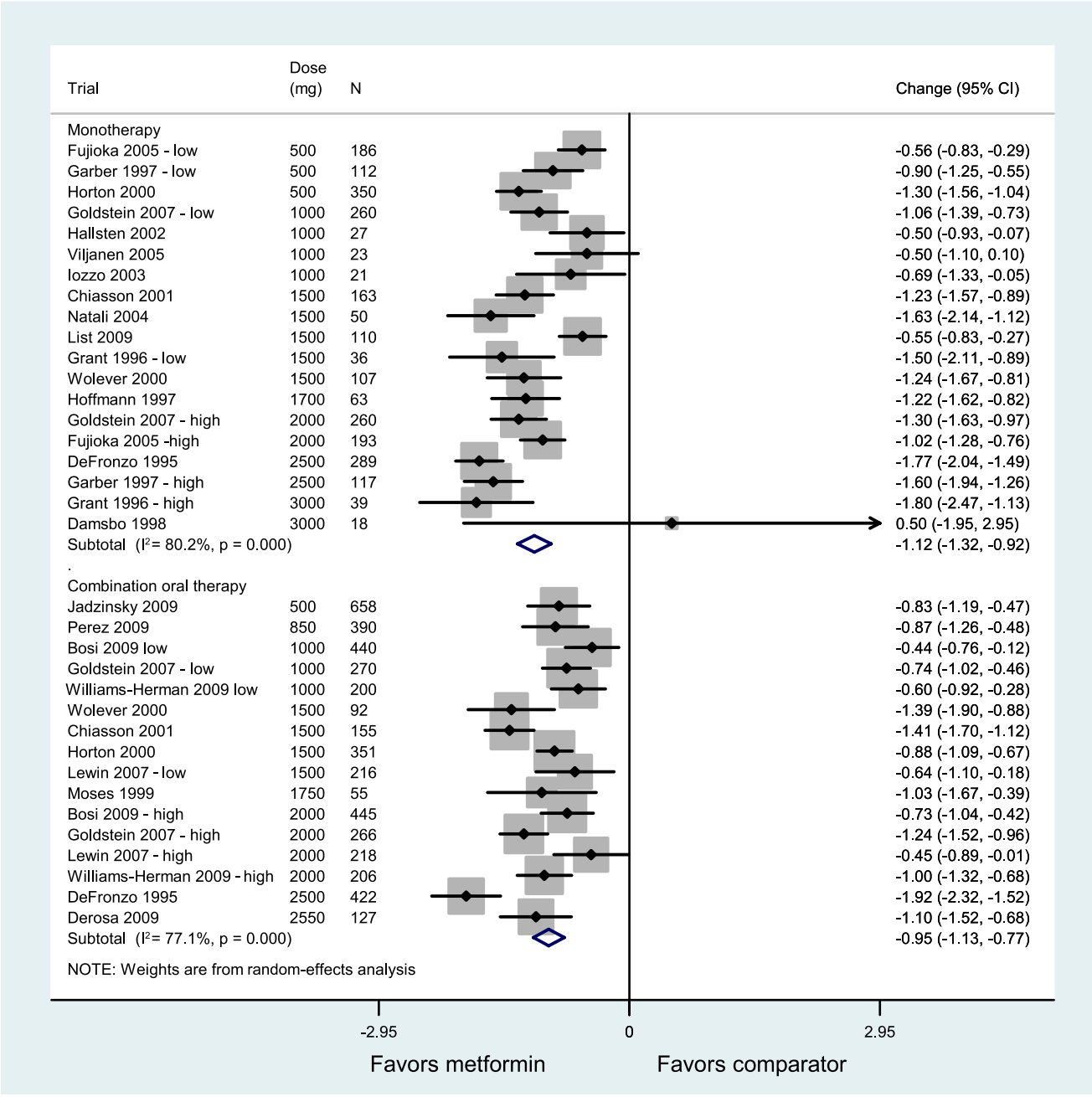

Figure 1—*Mean difference in change in HbA_{1c} of metformin treatment versus comparator (boxes) and pooled estimates (diamonds) calculated by the random-effects DerSimonian and Laird method, stratified by metformin monotherapy and metformin added to an oral antidiabetes medication. Horizontal bars and diamond widths denote 95% CIs, and box sizes indicate relative weight in the analysis. (A high-quality color representation of this figure is available in the online issue.)*

0.60% (95% CI 0.30–0.91; $P = 0.0001$, $I^2 = 79.8\%$), corresponding to a reduction of 6 mmol/mol more in the metformin groups than in the comparator group. A subgroup analysis of these trials performed on type of diabetes (Fig. 2) found that patients with type 2 diabetes taking metformin with their insulin treatment had HbA_{1c} levels 0.83% lower (0.48–1.18; $P = 0.000$, $I^2 = 74.2\%$) in nine trials, corresponding to HbA_{1c} of 9 mmol/mol lower than patients on insulin alone. Patients with type 1 diabetes, however, showed no change in their HbA_{1c} levels when metformin was added to their insulin treatment (change in HbA_{1c} −0.02% [95% CI −0.25 to 0.21]; $P = 0.43$, $I^2 = 0\%$) in four trials. Restricting the analysis to trials of ≥24 weeks included three trials of type 1 diabetes that gave no change in HbA_{1c} (−0.01% [−0.22 to 0.25]; $I^2 = 0\%$) and five trials of type 2 diabetes in which HbA_{1c} was 0.79% lower (95% CI 0.15–1.42; $I^2 = 83.4\%$) in metformin versus comparator groups.

Metaregression, carried out to investigate the effect of other variables and to explore sources of heterogeneity, found that no single factor could explain the heterogeneity. The I^2 statistic for the insulin trials was reduced by 24.3% by mean BMI. Year of publication reduced the I^2 by 11.8% for metformin combination trials and

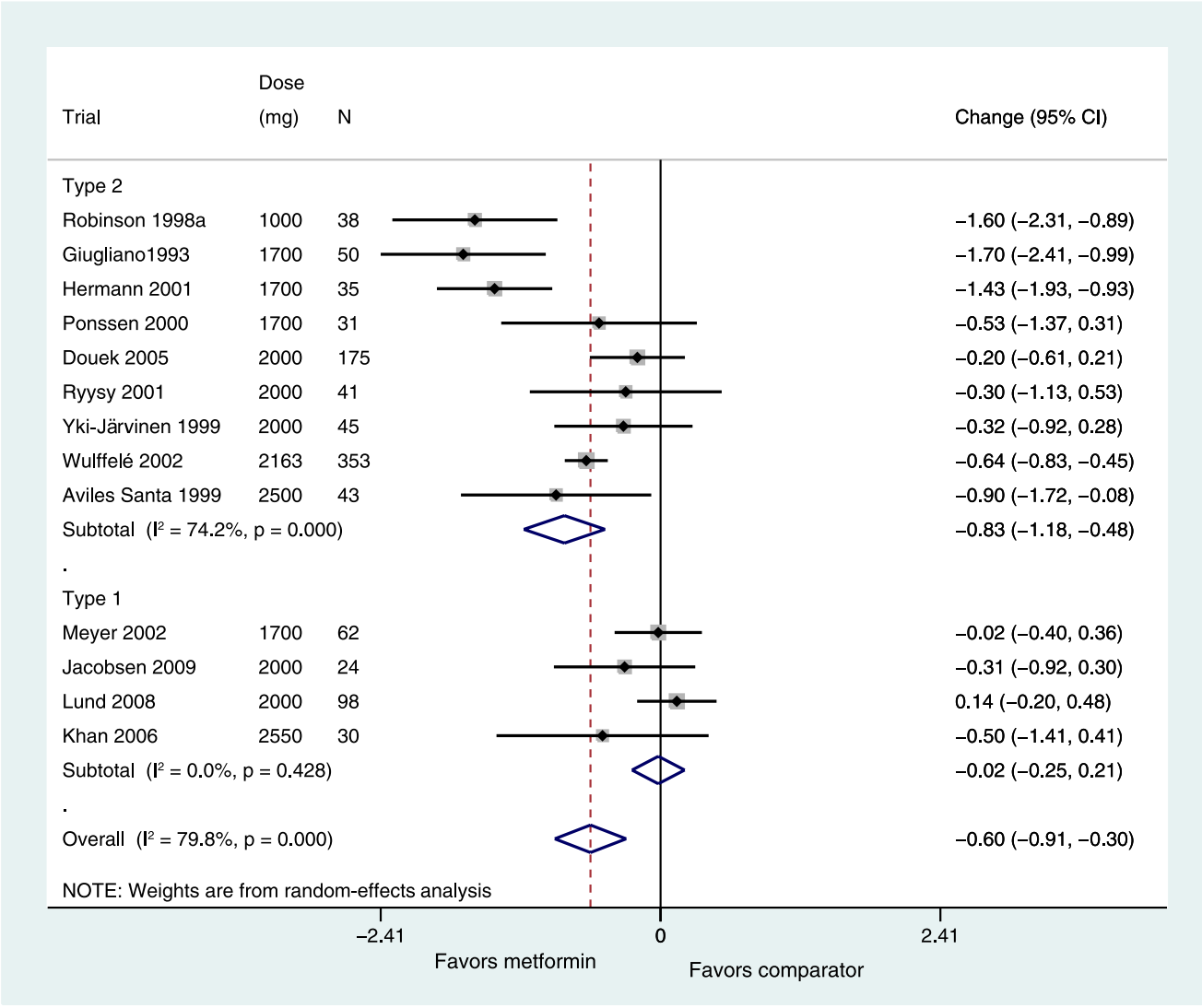

Figure 2—*Mean difference in change in HbA_{1c} of metformin added on to insulin versus placebo and insulin comparator (boxes) and pooled estimates (diamonds) calculated by the random-effects DerSimonian and Laird method, stratified by type of diabetes. Horizontal bars and diamond widths denote 95% CIs, and box sizes indicate relative weight in the analysis. (A high-quality color representation of this figure is available in the online issue.)*

18.5% for insulin trials. No other factor reduced heterogeneity by >10.4% in any of the analyses, even though year of publication, metformin dose, mean BMI, mean patient age, and mean duration of diabetes were significantly associated with the mean outcome in some of the analyses.

The dose-comparison review identified seven trials with head-to-head comparisons of two different metformin doses for inclusion, two of which could be used for more than one comparison, giving nine comparisons. Meta-analysis of data from these trials (Fig. 3) found significantly greater change in HbA_{1c} in the higher-dose arms with a reduction in HbA_{1c} of 0.26% (95% CI 0.14–0.38; $P < 0.0001$, $I^2 = 55.5\%$) more in these arms.

Adverse events

The most commonly reported adverse events were gastrointestinal events, such as diarrhea, nausea, vomiting, flatulence, and abdominal pain, but also included were hypoglycemia, dizziness, headache, urinary tract infection, hypertension, coughing, and palpitations. The meta-analysis of reported adverse events (Supplementary Fig. A2) found an increase in the number of adverse events in metformin-treated groups in comparison with comparator groups in the monotherapy trials (with an approximate risk ratio of 1.13 [95% CI 1.06–1.21]; $I^2 = 3\%$, $P = 0.0003$), and in oral combination trials (1.03 [0.95–1.12]; $I^2 = 82\%$, $P = 0.45$). The number of adverse events in insulin trials was not significantly different between the metformin group and the comparator group (2.37 [0.65–8.67]; $I^2 = 73\%$, $P = 0.19$). There was no significant difference in adverse events between higher and lower dose in the dose-comparison trials (approximate risk ratio = 1.23, $P = 0.13$). However, the assumption of independence was clearly an approximation (Supplementary Fig. A2).

An analysis of gastric adverse events (diarrhea and abdominal cramps) showed significantly more adverse events in the metformin arms of the monotherapy trials (approximate risk ratio 2.26 [95% CI 1.60–3.20]; $I^2 = 0\%$) and combination trials (1.55 [1.29–1.87]; $I^2 = 0\%$) and nonsignificantly more adverse events in the metformin arms of insulin trials (2.18 [0.68–7.01]; $I^2 = 78\%$). There were also more gastric

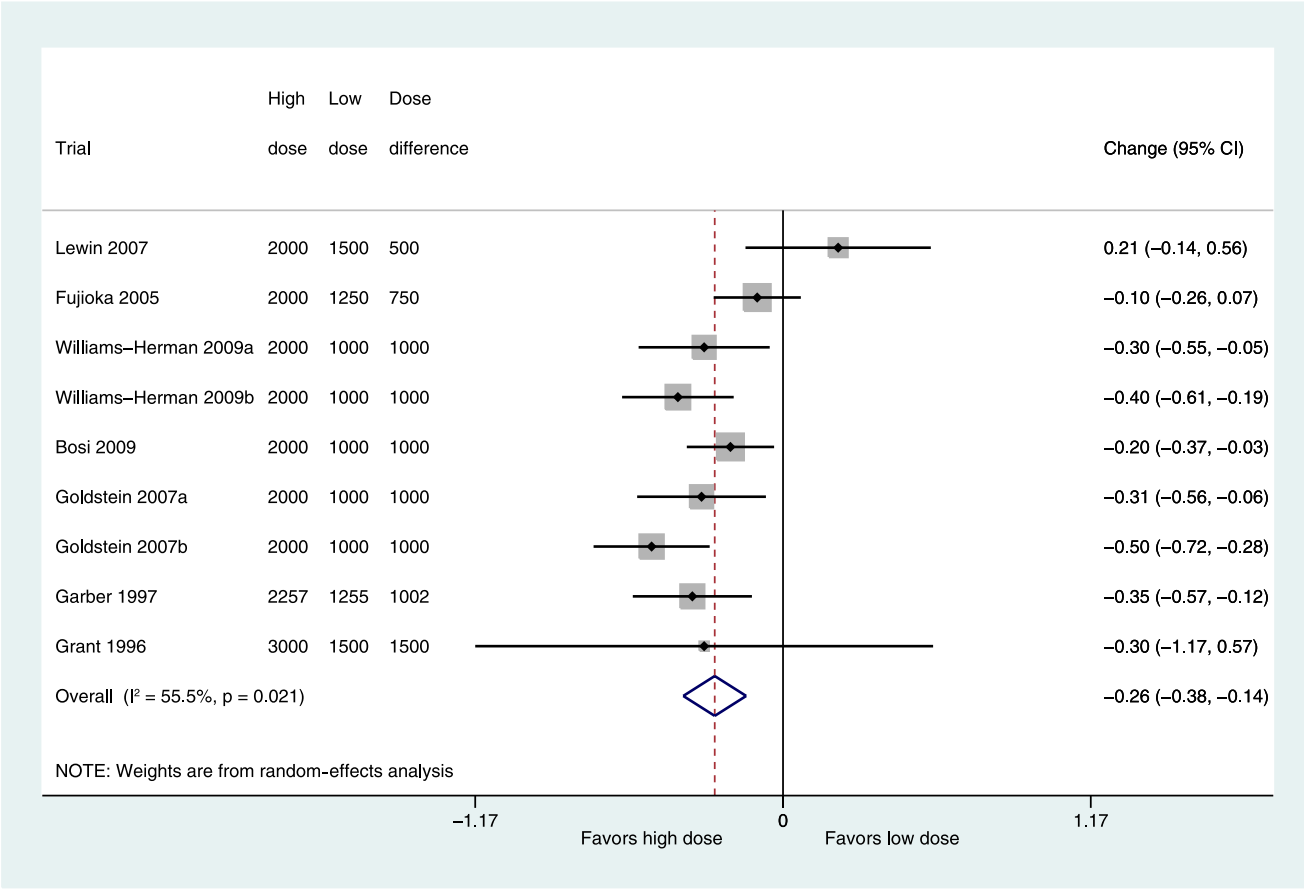

Figure 3—*Mean difference (boxes) in change in HbA_{1c} of high dose metformin, combining trial arms allocated to at least 2,000 mg metformin, versus low dose metformin, combining trial arms allocated to 1,000–1,500 mg metformin, showing pooled estimates (diamonds) calculated by the random-effects DerSimonian and Laird method. Horizontal bars and diamond widths denote 95% CIs, and box sizes indicate relative weight in the analysis. (A high-quality color representation of this figure is available in the online issue.)*

adverse events in the higher-dose trials compared with the lower-dose trials, although this was not significant (1.18 [0.98–1.42]; I^2 = 7%, P = 0.08).

CONCLUSIONS—This systematic review of double-blinded, randomized, controlled trials has separately examined metformin treatment as a stand-alone therapy and as an add-on therapy both to other oral medications and to insulin to quantify its effect on glycemic control. Metformin monotherapy reduced HbA_{1c} by 1.12%, and metformin in combination with other oral antihyperglycemic treatments or insulin reduced HbA_{1c} by 0.95 and 0.83%, respectively, for type 2 diabetes, and these effects were sustained at 24 weeks. Of particular interest is that the addition of metformin treatment to insulin treatment improves glycemic control in type 2 diabetes by a clinically significant level despite protocol-permitted insulin dose adjustments in both arms of these trials. Treatment of type 1 diabetic patients with metformin did not reduce HbA_{1c}. We have also clearly demonstrated that an increase in metformin dose results in a further modest reduction in HbA_{1c} of 0.26% in trials comparing lower doses to higher doses up to a metformin dose of 2,000 mg. It was not possible to establish whether there is further benefit when metformin dose is increased beyond this level because there were too few trials with higher doses, although the trial on which much of the evidence for cardiovascular benefit is based, the UK Prospective Diabetes Study (UKPDS) (16), used a median dose of 2,550 mg metformin. Establishing how the dose-effect relationship may vary at different doses and what the maximum effective dose may be is an area for future work.

A previous systematic review found lower rates of cardiovascular mortality in people randomized to metformin in six trials of >11,000 patients (6). Compared with that review, our analysis has the disadvantage of using the surrogate outcome of glucose lowering, albeit a well-established surrogate on which treatment guidelines are based (4,17,18), but it has the advantage of an estimate based on more trials. This has allowed us to examine subgroups, such as monotherapy, combination oral therapy, and insulin therapy, and to establish a dose-response relationship.

This is the most comprehensive systematic review to date on the effect of metformin treatment on HbA_{1c} levels. In addition, to our knowledge, this is the first meta-analysis of metformin dose-comparison studies. Significant unexplained heterogeneity observed between the trials, however, is a limitation of this review and, consequently, results need to be treated with caution. Our searches identified 5 times more trials than a previous review, which examined the effect of metformin on glycemic control in seven trials (8). This is partly explained by the other reviewer's more stringent inclusion criteria, which included a minimum of 50 subjects in each arm of the trial and an explicit

statement that informed consent was obtained. Inclusion of a larger number of trials has made it possible to separately analyze data from metformin monotherapy, oral combination therapy, and insulin trials. The greatest reduction in HbA_{1c} in our analysis was 1.1%, which is at the low end of the 1–2% estimated by Nathan et al. (3). The results of our review suggest that these estimated reductions are most likely to be achieved with the highest metformin doses. Previous trials that compared different metformin doses from various trials could not establish a dose-effect relationship of metformin (8). By including head-to-head trials of metformin in our systematic review, we clearly demonstrate the benefit of using a higher metformin dose to maximize HbA_{1c} reduction, although there may be an associated increase in gastric side effects. We have not been able to demonstrate a relationship between baseline HbA_{1c} and change in HbA_{1c} with treatment observed in other systematic reviews (8,19). A previous systematic review of 61 trials of oral glucose-lowering therapy found an association between baseline HbA_{1c} and the change in HbA_{1c} on treatment, but metformin was a randomized therapy in only seven of these trials (8). We were not able to find such a relationship in 15 trials of metformin monotherapy, 12 trials of metformin in combination with oral therapy, and 13 trials of metformin in combination with insulin. However, our analysis is based on metaregression, which compares mean values across trials. The best data to address this question would make comparisons between individuals (20). These results, therefore, need to be interpreted with caution.

Metformin's known benefit in reducing cardiovascular mortality (6), as well as its neutral effects on body weight and low risk of hypoglycemia (16), has led to wide recommendations for routine prescribing. However, until now, it has not been clear how different patients may respond to treatment. By separately examining the effect of metformin treatment in various groups of patients, depending on their previous antidiabetes medication, we are providing a tool to assist decisions on treatment combinations and optimal doses.

This review demonstrates that metformin treatment can be used to reduce HbA_{1c} in all patients with type 2 diabetes regardless of prior antihyperglycemic medication or insulin treatment. Use of higher doses of metformin resulted in modestly higher decreases in HbA_{1c} compared with lower doses. Metformin use in type 1 diabetes may not, however, reduce HbA_{1c}. Despite this, there may be other indications for treating type 1 diabetic patients with metformin because a reduction in insulin dose required in the metformin arm of these trials was observed consistent with metformin's role as an insulin sensitizer (21).

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J.A.H. researched data and wrote the manuscript. A.J.F. contributed to discussion and reviewed and edited the manuscript. R.A. and N.W.R. researched data and reviewed and edited the manuscript. R.J.S. researched data, contributed to discussion, and reviewed and edited the manuscript.

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