Long-term Effects of Metformin on Diabetes Prevention: Identification of Subgroups That Benefited Most in the Diabetes Prevention Program and Diabetes Prevention Program Outcomes Study

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OBJECTIVE

We examined the effects of metformin on diabetes prevention and the subgroups that benefited most over 15 years in the Diabetes Prevention Program (DPP) and its follow-up, the Diabetes Prevention Program Outcomes Study (DPPOS).

RESEARCH DESIGN AND METHODS

During the DPP (1996–2001), adults at high risk of developing diabetes were randomly assigned to masked placebo (n = 1,082) or metformin 850 mg twice daily (n = 1,073). Participants originally assigned to metformin continued to receive metformin, unmasked, in the DPPOS (2002–present). Ascertainment of diabetes development was based on fasting or 2-h glucose levels after an oral glucose tolerance test or on HbA_{1c}. Reduction in diabetes incidence with metformin was compared with placebo in subgroups by hazard ratio (HR) and rate differences (RDs).

RESULTS

During 15 years of postrandomization follow-up, metformin reduced the incidence (by HR) of diabetes compared to placebo by 17% or 36% based on glucose or HbA_{1c} levels, respectively. Metformin's effect on the development of glucose-defined diabetes was greater for women with a history of prior gestational diabetes mellitus (GDM) (HR 0.59, RD −4.57 cases/100 person-years) compared with parous women without GDM (HR 0.94, RD −0.38 cases/100 person-years [interaction P = 0.03 for HR, P = 0.01 for RD]). Metformin also had greater effects, by HR and RD, at higher baseline fasting glucose levels. With diabetes development based on HbA_{1c}, metformin was more effective in subjects with higher baseline HbA_{1c} by RD, with metformin RD −1.03 cases/100 person-years with baseline HbA_{1c} <6.0% (42 mmol/mol) and −3.88 cases/100 person-years with 6.0–6.4% (P = 0.0001).

CONCLUSIONS

Metformin reduces the development of diabetes over 15 years. The subsets that benefitted the most include subjects with higher baseline fasting glucose or HbA_{1c} and women with a history of GDM.

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**A complete list of centers, investigators, and staff can be found in the Supplementary Data online.*

A complete list of the members of the writing committee can be found in the Appendix.

See accompanying article, p. 499.

PATHOPHYSIOLOGY/COMPLICATIONS

The Diabetes Prevention Program (DPP) (1) and its follow-up, the Diabetes Prevention Program Outcomes Study (DPPOS) (2,3), have demonstrated the beneficial effects of the diabetes medication metformin to reduce the risk of developing diabetes. The DPP was conducted in a cohort at high risk for the development of diabetes on the basis of having impaired glucose tolerance, elevated fasting glucose levels, and being at least overweight. In the original DPP trial, analyzed after an average of 2.8 years of follow-up, metformin was of particular benefit in those persons who at baseline had higher fasting glucose levels (110–125 vs. 95–109 mg/dL) or a BMI ≥35 kg/m^2 (vs. 24 to <35 kg/m^2) (1). In addition, women with a self-reported history of gestational diabetes mellitus (GDM) had a greater benefit from metformin than parous women without such a history (4).

Whether metformin should be used for diabetes prevention requires a careful balance of benefits and risks. The American Diabetes Association has endorsed its use for this purpose, recommending that "metformin therapy for prevention of type 2 diabetes should be considered in those with prediabetes, especially for those with BMI ≥35 kg/m^2, those aged <60 years, women with prior gestational diabetes mellitus, and/or those with rising A1C despite lifestyle intervention" (5).

To inform the discussion regarding metformin for prevention, we have analyzed the 15-year results from DPP/DPPOS to determine the longer-term effects of metformin on diabetes prevention and, in particular, prevention in the subgroups that appeared to benefit most from metformin during the DPP. Since glycated hemoglobin (HbA$_{1c}$) levels are increasingly used to identify persons at risk for or with diabetes (6), rather than fasting glucose and glucose tolerance testing as was used in DPP/DPPOS, we analyzed the effects of metformin on diabetes development in subgroups, as described above, using HbA$_{1c}$ values, applied post hoc, as well as glucose-based diagnostic levels to diagnose diabetes (7).

RESEARCH DESIGN AND METHODS

The design and methods of the DPP and DPPOS have previously been described in detail (1–3,8).

Participants and Procedures

In brief, between 1996 and 1999, the DPP enrolled 3,234 participants aged ≥25 years who were at high risk of developing diabetes based on having impaired glucose tolerance, elevated fasting blood glucose 95 to 125 mg/dL (≤125 mg/dL in the American Indian centers), and a BMI ≥24 kg/m^2 (≥22 kg/m^2 in Asian Americans). HbA$_{1c}$ was measured throughout DPP and DPPOS but was not an eligibility criterion. Participants were randomly assigned to placebo (n = 1,082), metformin titrated to 850 mg twice daily (n = 1,073), or intensive lifestyle intervention (n = 1,079). All DPP participants randomized to the metformin and placebo treatment groups (total n = 2,155) are considered in this publication (Table 1). Written informed consent was obtained from all participants, and the studies were approved by each clinical center's institutional review board.

After DPP ended in 2001, all participants were offered a group-administered version of the lifestyle curriculum. Eighty-six percent (n = 1,861) of the surviving members of the metformin and placebo treatment groups volunteered to continue follow-up in the DPPOS. Placebo was discontinued, and those previously assigned to metformin continued to receive metformin 850 mg twice daily, now unmasked. Metformin was discontinued if diabetes was diagnosed and fasting glucose level was ≥140 mg/dL during DPP (or HbA$_{1c}$ was ≥7% [53 mmol/mol] during DPPOS), which resulted in referral to the participant's own physician for further management (2). Many such patients were subsequently treated with metformin by their own health care providers.

Measures

Diagnosis of diabetes during DPP and DPPOS was based on the annual oral glucose tolerance test (OGTT) or semiannual fasting plasma glucose (FPG) tests, using the 1997 American Diabetes Association diagnostic criteria (fasting ≥126 mg/dL or 2-h glucose ≥200 mg/dL during a 75-g OGTT), with the diagnosis requiring confirmation with repeat testing (9). In a previous analysis (7), diagnosis of diabetes was also determined post hoc based on HbA$_{1c}$ ≥6.5%. In the analyses with HbA$_{1c}$ as the diagnostic outcome, participants who had diabetes at baseline based on HbA$_{1c}$ ≥6.5% (48 mmol/mol) or fasting glucose 126–139 mg/dL (the original inclusion criteria included a FPG 100–139 mg/dL between 1996 and June 1997 [10], which was subsequently changed to 95–125 mg/dL) were excluded. This leaves 1,833 of the original DPP participants in the combined metformin and placebo treatment groups for the analyses herein that use HbA$_{1c}$ as the diabetes diagnostic outcome (Table 1).

Statistical Analyses

The current analyses cover an average of 15 years of DPP and DPPOS: participants were recruited from 1996–1999 and followed through the end of 2013. We identified subgroups of interest a priori based on sex, race/ethnicity, and baseline age, BMI, and fasting and 2-h postload plasma glucose and HbA$_{1c}$ levels and a self-reported history of GDM in parous women (1,4,7). Time to diabetes defined by glucose levels or by HbA$_{1c}$ compared metformin with placebo on a modified product-limit life table distribution with a log-rank test statistic, overall and within subgroup (11). Follow-up was censored at the participant's last visit, regardless of DPPOS participation, if diabetes had not developed. Proportional hazards regression models were used to estimate hazard ratios (HRs) and assess heterogeneity. A likelihood ratio test of two models was used with and without the interaction term between treatment assignments and covariates (in continuous form for age, BMI, and glycemia). Rate difference (RD) on an absolute scale between the metformin and placebo groups was expressed in cases per 100 person-years based on treatment-specific crude rates calculated as the number of diabetes events divided by the total number of person-years of follow-up under a doubly homogenous Poisson model. This provides a linearized rate estimate over the total follow-up period (11). Heterogeneity in risk differences among subgroups was assessed using a composite Wald test (11). DPP and DPPOS have generally had low rates of missing data. Visit completion rates (~87% of those enrolled) did not differ among the three treatment groups, and missing data were assumed to be missing at random. A $P \leq 0.05$ was considered significant.

RESULTS

The baseline characteristics of the metformin and placebo-assigned participants

Table 1—Characteristics of participants in metformin and placebo groups at DPP baseline (1996–1999)

	Cohort for glucose-based diagnoses			Cohort for HbA_{1c}-based diagnoses		
	Total (*N* = 2,155)	Placebo (*N* = 1,082)	Metformin (*N* = 1,073)	Total (*N* = 1,833)	Placebo (*N* = 922)	Metformin (*N* = 911)
Age (yr)						
Mean ± SD	50.6 ± 10.4	50.3 ± 10.4	50.9 ± 10.3	50.3 ± 10.3	50.1 ± 10.4	50.4 ± 10.2
25–44	642 (29.8)	324 (29.9)	318 (29.6)	562 (30.7)	283 (30.7)	279 (30.6)
45–59	1,098 (51.0)	557 (51.5)	541 (50.4)	934 (51)	468 (50.8)	466 (51.2)
≥60	415 (19.3)	201 (18.6)	214 (19.9)	337 (18.4)	171 (18.5)	166 (18.2)
Female	1,457 (67.6)	747 (69.0)	710 (66.2)	1,249 (68.1)	643 (69.7)	606 (66.5)
Parous women						
No history of GDM	951 (80.3)	487 (80.0)	464 (80.6)	818 (80.4)	422 (80.2)	396 (80.5)
History of GDM	233 (19.7)	122 (20.0)	111 (19.3)	200 (19.6)	104 (19.8)	96 (19.5)
Race/ethnicity						
Non-Hispanic white	1,188 (55.1)	586 (54.2)	602 (56.1)	1,087 (59.3)	539 (58.5)	548 (60.2)
African American	441 (20.4)	220 (20.3)	221 (20.6)	287 (15.7)	140 (15.2)	147 (16.1)
Hispanic	330 (15.3)	168 (15.5)	162 (15.1)	290 (15.8)	151 (16.4)	139 (15.3)
American Indian	111 (5.2)	59 (5.5)	52 (4.8)	97 (5.3)	50 (5.4)	47 (5.2)
Asian/Pacific Islander	85 (3.9)	49 (4.5)	36 (3.4)	72 (3.9)	42 (4.6)	30 (3.3)
BMI (kg/m^2)						
Mean ± SD	34.0 ± 6.6	34.1 ± 6.7	33.9 ± 6.6	33.7 ± 6.5	33.8 ± 6.5	33.6 ± 6.4
<30	689 (32.0)	340 (31.4)	349 (32.5)	603 (32.9)	300 (32.5)	303 (33.3)
30 to <35	658 (30.5)	315 (29.1)	343 (32.0)	574 (31.3)	276 (29.9)	298 (32.7)
≥35	808 (37.5)	427 (39.5)	381 (35.5)	656 (35.8)	346 (37.5)	310 (34)
Fasting glucose (mg/dL)						
Mean ± SD	106.6 ± 8.4	106.7 ± 8.4	106.5 ± 8.5	105.4 ± 7.4	105.6 ± 7.4	105.2 ± 7.4
95–109	1,440 (66.8)	726 (67.1)	714 (66.5)	1,324 (72.2)	663 (71.9)	661 (72.6)
110–125*	715 (33.2)	356 (32.9)	359 (33.5)	509 (27.8)	259 (28.1)	250 (27.4)
2-h glucose (mg/dL)						
Mean ± SD	164.8 ± 17.2	164.5 ± 17.1	165.1 ± 17.2	164.0 ± 16.9	163.8 ± 16.9	164.3 ± 17.0
140–153	699 (32.8)	360 (33.3)	339 (31.6)	617 (33.7)	315 (34.2)	302 (33.2)
154–172	730 (34.3)	374 (34.6)	356 (33.2)	633 (34.5)	328 (35.6)	305 (33.5)
173–199	726 (33.7)	348 (32.2)	378 (35.2)	583 (31.8)	279 (30.3)	304 (33.4)
HbA_{1c}						
Mean ± SD (%)	5.9 ± 0.50	5.9 ± 0.51	5.9 ± 0.50	5.8 ± 0.39	5.8 ± 0.4	5.8 ± 0.4
<6% (42 mmol/mol)	1,168 (54.3)	578 (53.6)	590 (55.1)	1,161 (63.3)	576 (62.5)	585 (64.2)
6–6.4% (42–46 mmol/mL)	982 (45.7)	501 (46.4)	533 (49.7)	672 (36.7)	346 (37.5)	326 (35.8)

Data are *n* (%) unless otherwise indicated. yr, years. *Thirty-eight participants who were recruited prior to the American Diabetes Association change in diagnostic criteria (9) had fasting glucose levels between 125 and 139 mg/dL at baseline.

(1,082 placebo and 1,073 metformin) and the subset included in the HbA_{1c} analyses are shown in Table 1. The consort diagram for this population followed over time has previously been published (3).

Through 15 years, the mean cumulative exposure to metformin in the original DPP participants assigned to metformin was 8.75 years (9,389.5 years of exposure/1,073 persons = 8.75 years/person) compared with 1.71 years (1,848.5 years/1,082 persons = 1.71 years/person) in the original placebo group (Supplementary Fig. 1). The metformin exposure in the placebo group was almost entirely owing to treatment with nonstudy metformin after the development of diabetes. During this time, the metformin treatment group had a 17% lower incidence of diabetes development than the placebo group (HR 0.83 [95% CI 0.73–0.93], RD −1.25 cases/100 person-years [95% CI −2.01 to −0.49]) based on fasting and/or 2-h glucose results (Fig. 1 and Table 2). With HbA_{1c} used as the diagnostic outcome for diabetes, metformin was associated with a 36% reduction in risk (HR 0.64 [95% CI 0.55–0.75]) or an RD of −1.67 cases/100 person-years (95% CI −2.24 to −1.10) (Fig. 2 and Table 2).

The analyses of the effects of metformin on diabetes development over 15 years in subgroups are shown for glucose-based diabetes in Table 2 and Fig. 1 and for HbA_{1c}-based diabetes in Table 2 and Fig. 2. Based on RDs and HRs when using glucose levels for diagnosis, there were no significant interactions with baseline age, sex, race/ethnicity, BMI, 2-h plasma glucose, or HbA_{1c} levels. The metformin group had a greater effect at higher baseline FPG (interaction P = 0.02 for RD and P = 0.0004 for HR). Of note, the different effects of metformin by age seen in the original analyses after ~3 years of DPP were no longer seen by age-group (25–45, 45–59, and ≥60 years of age) (Table 2). With age considered as a continuum, the interaction was not statistically significant (interaction P = 0.08 for the RD). Although the interactions with age were not significant, when considered in isolation the oldest age-group had no benefit with metformin when glucose was used for diagnosis (HR 1.04 [absolute rate was higher in the metformin group by 0.35 cases/100 person-years]) (Fig. 1). By contrast, in the youngest age-group (25–45 years), the HR was 0.73 and the RD was −2.2 cases/100 person-years (Table 2). Similarly, the interactions for the HR and RD were not

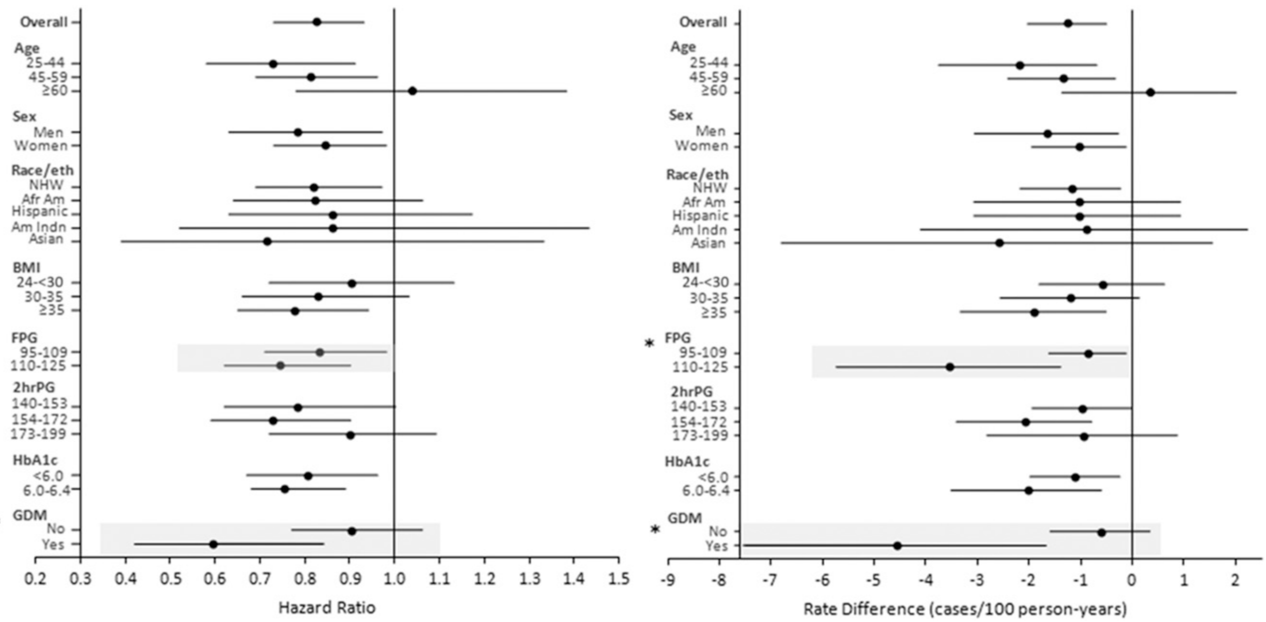

Figure 1—Forest plot of diabetes HRs and hazard RDs with diabetes defined by glucose levels for metformin vs. placebo over 15 years by subgroups defined at DPP baseline. Point estimates and 95% CIs shown. Highlighted rows show significant treatment-by-group interactions. Group interactions were tested using continuous values for baseline values of age (years), BMI (kg/m^2), FPG and 2-h glucose (2hrPG) (mg/dL), and HbA_{1c} (%). Statistically significant ($P < 0.05$) interactions of metformin treatment by subgroup are indicated by shading and as follows: *FPG-by-treatment interaction P = 0.02, GDM-by-treatment interaction P = 0.01; ‡FPG-by-treatment interaction $P < 0.001$, GDM-by-treatment interaction P = 0.02. Afr Am, African American; Am Indn, American Indian; eth, ethnicity; GDM, history of prior GDM; NHW, non-Hispanic white.

significant for BMI, indicating no difference in the metformin benefit by BMI. However, considered in isolation, only the highest BMI group had a significant benefit with metformin. History of GDM had a significant interaction with metformin effect on HR (interaction P = 0.03), with a 41% reduction (HR 0.59) in diabetes development for metformin versus placebo in women with a self-reported history of GDM but a nonsignificant 6% reduction (HR 0.94) in parous women who did not report a history of GDM. The GDM-by-treatment interaction was even more pronounced when analyzed by RD, with metformin reducing diabetes incidence by 4.57 cases/100 person-years in women with a history of GDM compared with only 0.38 in women without such a history (interaction P = 0.01).

When the outcome was diabetes defined by HbA_{1c}, there were no statistically significant interactions using HRs of diabetes development with metformin compared with placebo among the subgroups defined by demographic characteristics or any of the preselected clinical variables. Metformin was equally effective in women with or without a history of GDM history (Fig. 2 and Table 2). Therefore, compared with placebo, metformin had comparable beneficial effects by HR across all of the subgroups when HbA_{1c} was used as the outcome. However, while the effect of metformin was nearly identical in those with baseline HbA_{1c} <6.0% (42 mmol/mol) vs. 6.0% to 6.4% (42–46 mmol/mol) based on HRs (0.61 and 0.63, respectively), there was substantial heterogeneity if the absolute difference in cases was used (RDs −1.03 and −3.88 cases/100 person-years, respectively, interaction P = 0.001).

Ideally, we could have explored heterogeneity in various combinations of the baseline factors, but the number of cases and participants in the individual cells were generally too small to allow reliable estimates of the metformin effect for many of the combinations. We therefore restricted these exploratory analyses of baseline factor combinations in those with heterogeneity (namely, GDM status and fasting glucose) and with age (Supplementary Tables 1 and 2).

For example, Fig. 1 and Table 2 show that in those with fasting glucose ≥110 mg/dL, metformin led to a much greater risk difference (RD −3.53 cases/100 person-years) than in those with lower fasting glucose (RD −0.86), and there was a much greater risk difference in women with than those without a history of GDM. These observations raise the question of effects in combinations, such as higher fasting glucose (associated with greater benefit) among women without a history of GDM (associated with less benefit). Supplementary Table 1 suggests approximate additivity of these effects in that the least benefit (RD −0.15) was in women with no history of GDM and lower fasting glucose and the greatest benefit (RD −10.13) occurred in women with a history of GDM and higher fasting glucose. Women in whom one of these factors indicated higher risk and the other indicated lower risk derived intermediate benefit (RD −3.65 or −3.40). These differences in risk differences with metformin were statistically significant (P = 0.008 for interaction of metformin with the subgroups). The interactions of metformin with the other subgroups shown in Supplementary Tables 1 and 2 were not statistically significant, albeit many of the subgroups were small, affording little power for analyses of such combinations.

CONCLUSIONS

Previous analyses of the original DPP data supported a particularly powerful effect

Table 2—Metformin treatment effects on diabetes defined by fasting or 2-h postload glucose or by HbA_{1c} ≥6.5%

Subgroup	*N*	%	PLAC rate (cases/ 100 pyr)	MET rate (cases/ 100 pyr)	HR (95% CI) for MET vs. PLAC	Subgroup-by-MET *P*	RD (95% CI), cases/100 pyr	Subgroup-by-MET *P*
Diabetes defined by fasting or 2-h PG								
Overall	2,155	100.0	7.14	5.89	0.83 (0.73–0.93)		−1.25 (−2.01 to −0.49)	
Age, years						0.17		0.08
25 to <45	642	29.8	8.19	5.99	0.73 (0.58–0.91)		−2.2 (−3.72 to −0.68)	
45 to <60	1,098	51.0	7.04	5.69	0.81 (0.69–0.96)		−1.35 (−2.39 to −0.32)	
≥60	415	19.3	5.93	6.28	1.04 (0.78–1.38)		0.35 (−1.33 to 2.02)	
Sex						0.55		0.46
Men	698	32.4	7.49	5.85	0.78 (0.63–0.97)		−1.64 (−3.03 to −0.26)	
Women	1,457	67.6	6.99	5.90	0.85 (0.73–0.98)		−1.02 (−1.93 to −0.11)	
Race/ethnicity						0.99		0.97
Non-Hispanic white	1,188	55.1	6.52	5.34	0.82 (0.69–0.97)		−1.18 (−2.15 to −0.22)	
African American	441	20.5	8.84	7.32	0.82 (0.64–1.06)		−1.52 (−3.49 to 0.45)	
Hispanic	330	15.3	7.19	6.15	0.86 (0.63–1.17)		−1.04 (−3.03 to 0.94)	
American Indian	111	5.2	6.82	5.94	0.86 (0.52–1.43)		−0.89 (−4.01 to 2.24)	
Asian/South Pacific Islander	85	3.9	8.37	5.79	0.72 (0.39–1.33)		−2.58 (−6.72 to 1.56)	
BMI, kg/m^2						0.25		0.37
24 to <30	689	32.0	5.80	5.22	0.90 (0.72–1.13)		−0.58 (−1.78 to 0.63)	
30 to <35	658	30.5	6.83	5.64	0.83 (0.66–1.03)		−1.19 (−2.53 to 0.14)	
≥35	808	37.5	8.67	6.77	0.78 (0.65–0.94)		−1.9 (−3.30 to −0.50)	
FPG, mg/dL						0.0004		0.02
95–109	1,440	66.8	5.13	4.28	0.83 (0.71–0.98)		−0.86 (−1.6 to −0.11)	
≥110	715	33.2	14.10	10.60	0.75 (0.62–0.90)		−3.53 (−5.69 to −1.38)	
2-h PG, mg/dL						0.60		0.37
140–153	699	32.4	4.47	3.51	0.78 (0.62–1.00)		−0.96 (−1.92 to 0)	
154–172	730	33.9	7.46	5.38	0.73 (0.59–0.90)		−2.08 (−3.38 to −0.78)	
173–199	726	33.7	10.7	9.74	0.90 (0.72–1.09)		−0.95 (−2.78 to 0.88)	
HbA_{1c}, % (mmol/mol)						0.26		0.27
<6.0 (42)	1,168	62.9	5.57	4.47	0.81 (0.67–0.96)		−1.10 (−1.96 to −0.23)	
6.0–6.4 (42–46)	688	37.1	8.26	6.22	0.76 (0.68–0.89)		−2.03 (−3.48 to −0.59)	
GDM among parous women						0.02		0.01
No	951	80.3	6.33	5.95	0.94 (0.78–1.13)		−0.39 (−1.48 to 0.71)	
Yes	233	19.7	11.1	6.48	0.59 (0.42–0.84)		−4.57 (−7.48 to −1.67)	
Diabetes defined by HbA_{1c} ≥6.5%								
Overall	1,833	100.0	4.53	2.86	0.64 (0.55–0.75)		−1.67 (−2.24 to −1.1)	
Age, years						0.67		0.82
25 to <45	564	30.7	5.16	3.53	0.68 (0.52–0.90)		−1.63 (−2.8 to −0.46)	
45 to <60	936	51.0	4.29	2.74	0.65 (0.52–0.81)		−1.56 (−2.32 to −0.79)	
≥60	337	18.3	4.27	2.25	0.55 (0.37–0.82)		−2.02 (−3.26 to −0.77)	
Sex						0.08		0.06
Men	586	31.9	5.21	2.67	0.52 (0.39–0.69)		−2.53 (−3.61 to −1.46)	
Women	1,251	68.1	4.26	2.96	0.70 (0.58–0.85)		−1.3 (−1.98 to −0.62)	
Race/ethnicity						0.86		0.46
Non-Hispanic white	1,090	59.3	3.61	2.31	0.64 (0.52–0.81)		−1.31 (−1.96 to −0.66)	
African American	288	15.7	7.91	5.23	0.67 (0.48–0.95)		−2.67 (−4.82 to −0.52)	
Hispanic	290	15.8	4.86	3.20	0.66 (0.45–0.97)		−1.67 (−3.17 to −0.16)	
American Indian	97	5.3	5.39	2.96	0.54 (0.28–1.04)		−2.42 (−5.01 to 0.17)	
Asian/Pacific Islander	72	3.9	5.83	2.30	0.42 (0.18–1.00)		−3.53 (−6.6 to −0.46)	
BMI (kg/m^2)						0.34		0.88
24 to <30	605	32.9	3.56	2.11	0.60 (0.44–0.81)		−1.45 (−2.3 to −0.61)	
30 to <35	575	31.3	4.39	2.68	0.62 (0.46–0.82)		−1.71 (−2.71 to −0.71)	
≥35	657	35.8	5.65	3.88	0.70 (0.55–0.89)		−1.77 (−2.89 to −0.65)	
FPG, mg/dL						0.04		0.08
95–109	1,328	72.3	3.55	2.18	0.62 (0.50–0.76)		−1.37 (−1.95 to −0.8)	
≥110	509	27.7	7.92	5.04	0.66 (0.51–0.85)		−2.88 (−4.46 to −1.3)	
2-h PG, mg/dL						0.91		0.71
140–153	619	33.7	3.64	2.23	0.62 (0.46–0.84)		−1.41 (−2.26 to −0.56)	
154–172	634	34.5	4.76	2.97	0.64 (0.49–0.83)		−1.79 (−2.79 to −0.79)	
173–199	584	31.8	5.40	3.43	0.64 (0.49–0.84)		−1.97 (−3.12 to −0.82)	

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Table 2—Continued

Subgroup	N	%	PLAC rate (cases/100 pyr)	MET rate (cases/100 pyr)	HR (95% CI) for MET vs. PLAC	Subgroup-by-MET P	RD (95% CI), cases/100 pyr	Subgroup-by-MET P
HbA_{1c}, % (mmol/mol)	1,161	63.3	2.70	1.67		0.057		0.001
<6.0 (42)	672	36.7	9.53	5.65	0.61 (0.48–0.78)		−1.03 (−1.55 to −0.51)	
6.0–6.4 (42–46)	1,161	63.3	2.70	1.67	0.63 (0.51–0.78)		−3.88 (−5.43 to −2.32)	
GDM among parous women						0.21		0.13
No	818	80.4	4.14	2.97	0.73 (0.57–0.92)		−1.17 (−2.01 to −0.34)	
Yes	200	19.6	5.80	2.97	0.52 (0.33–0.83)		−2.82 (−4.78 to −0.87)	

MET, metformin; PG, postload glucose; PLAC, placebo; pyr, person-years.

of metformin in subgroups defined by higher fasting glucose levels, higher BMI, and a history of GDM, when evaluated by percent risk reduction, i.e., the HR for metformin compared with placebo. These results prompted the American Diabetes Association (5), among others (12–16), to suggest that metformin be considered in the prevention of diabetes in people at high risk. The American Diabetes Association specifically recommended that metformin be considered in those subgroups that it concluded had the greatest relative benefit with metformin in the DPP. This recommendation is further supported by the demonstrated cost savings of metformin in diabetes prevention (17).

Examining treatment interactions in terms of the heterogeneity of HRs does not give the full picture needed to decide which sets of persons are likely to derive more or less benefit from the intervention. One should also consider the absolute differences in incidence rates among groups, i.e., RDs. Under homogeneity of treatment effects on HRs, the RDs (metformin vs. placebo) are greater in groups with higher underlying rates and lower in groups with lower underlying rates. For example, in a subgroup with a very low rate of progression to disease, there is little room for improvement in absolute rates even if the HR produced by the treatment is the same as in the high-risk groups. The strongest example of this in the current study is the interaction of baseline HbA_{1c} with diabetes when the outcome is defined by HbA_{1c} (Table 1 and Fig. 1*B*). There is no heterogeneity using the HR (HRs of 0.61 and 0.63 in the low and high baseline HbA_{1c} groups, respectively), but the treatment effects on an absolute scale differ substantially (RDs due to metformin = −1.03 and −3.88 cases/100 person-years in the two groups, respectively, interaction P = 0.001). By this measure, public health treatment decisions regarding the use of metformin in patients with prediabetes should prioritize those with higher baseline HbA_{1c}.

We observed differences in the absolute rates of diabetes development using glucose-defined versus HbA_{1c}-defined diabetes. During DPP/DPPOS, most diabetes development was diagnosed based on the 2-h glucose level in the OGTT. HbA_{1c} was not yet a generally accepted method of diagnosis during the DPP study period, and we considered it a diabetes-defining outcome only in post hoc analyses. The OGTT, fasting glucose levels, and HbA_{1c} measure different aspects of glucose metabolism. The 2-h glucose level largely reflects glucose disposal into the insulin-sensitive peripheral tissues, predominantly muscle, while the fasting glucose level and HbA_{1c} are measures of hepatic glucose output and overall mean glycemia, respectively. Metformin is known to have its major effects by reducing hepatic glucose production, thereby lowering overnight glycemia and fasting glucose (18), the latter an important contributor to the HbA_{1c}. These effects are consistent with the relatively greater effect of metformin on HbA_{1c}-defined diabetes that we have shown here, including among subgroups that showed somewhat less beneficial effects with glucose-defined diabetes.

Whether the glucose-based results or HbA_{1c}-based results should be given greater credence is complicated. On the one hand, glucose-based results were used for eligibility and outcomes during the study and the selection of participants with baseline HbA_{1c} <6.5% (48 mmol/mol) for the current analyses was performed post hoc. Thus, the participants in our analysis represent a subset of those first selected based on their glucose-defined prediabetes, with HbA_{1c} criteria applied subsequently. This adversely affects the generalizability of the HbA_{1c} results and represents the major limitation of these analyses. On the other hand, in many countries, OGTTs are not used routinely for the identification of persons at high risk for diabetes or with diabetes. Therefore, the HbA_{1c} results may be more clinically relevant.

In summary, regardless of the means by which diabetes is diagnosed, the long-term effects of metformin on diabetes development in DPP/DPPOS suggest that metformin remains effective in this cohort. We have identified specific subgroups where metformin's effect was enhanced, namely, those with higher baseline fasting glucose or HbA_{1c} and women reporting a history of GDM. These results should help to prioritize those groups at high risk of developing diabetes who will benefit most from being treated with metformin. The conclusions regarding HbA_{1c} must be considered carefully, as our original eligibility and diabetes development criteria were based on glucose and not HbA_{1c} criteria. Continuing the follow-up for other outcomes, including incidence of microvascular disease, cancer, and cardiovascular disease, will provide information on other putative long-term benefits of metformin and whether they are homogeneous across subgroups.

Appendix

The writing committee was as follows: David M. Nathan (chair), William C. Knowler, Sharon L. Edelstein, Jill P. Crandall,

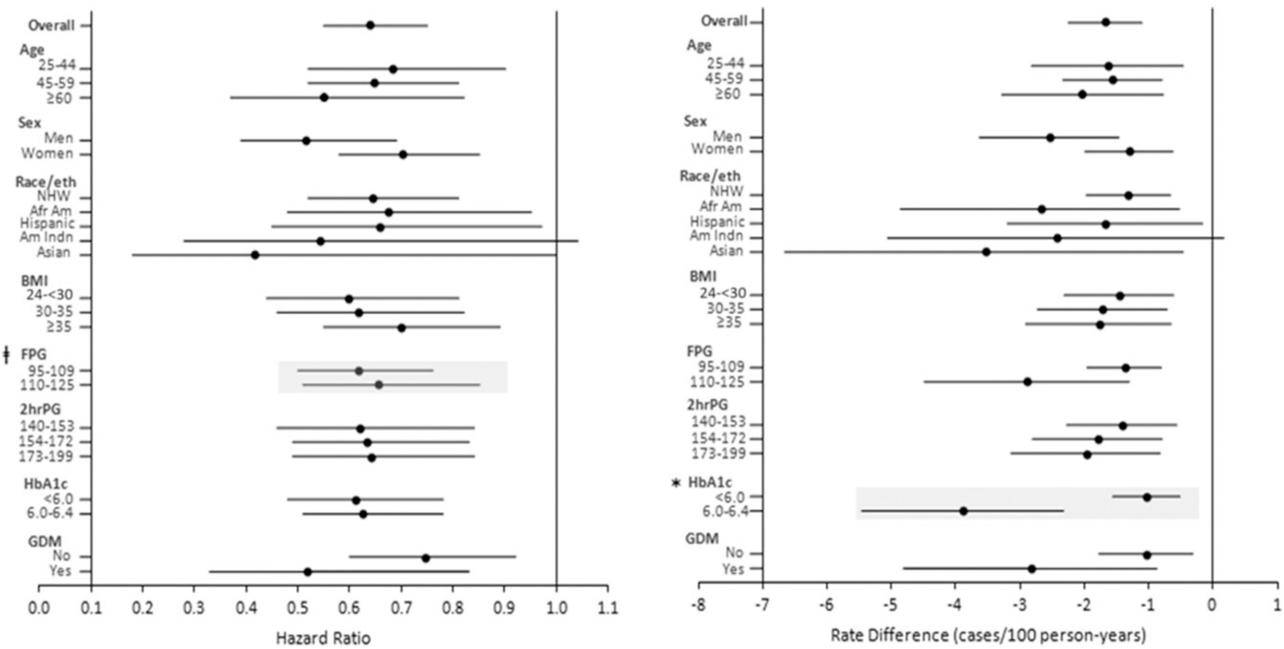

Figure 2—Forest plot of diabetes HRs and hazard RDs with diabetes defined by HbA_{1c} levels for metformin vs. placebo over 15 years by subgroups defined at DPP baseline. Point estimates and 95% CIs shown. Highlighted rows show significant treatment-by-group interactions. Group interactions were tested using continuous values for baseline values of age (years), BMI (kg/m^2), FPG and 2-h glucose (2hrPG) (mg/dL), and HbA_{1c} (%). Statistically significant ($P < 0.05$) interactions of metformin treatment by subgroup are indicated by shading and as follows: *HbA_{1c}-by-treatment interaction P = 0.001; ‡FPG-by-treatment interaction P = 0.04. Afr Am, African American; Am Indn, American Indian; eth, ethnicity; GDM, history of prior GDM; NHW, non-Hispanic white.

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The sponsor of this study was represented on the Steering Committee and played a part in study design, how the study was done, and publication.

The opinions expressed are those of the investigators and do not necessarily reflect the views of the funding agencies. The funding agencies were not represented on the writing group, although all members of the Steering Committee had input into the report's contents. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Author Contributions. D.M.N. researched data, wrote the first draft of the manuscript, and contributed to discussion. W.C.K., J.P.C., D.D., R.B.G., S.E.K., K.J.M., X.P.-S., G.T., and E.A.W. researched data, contributed to discussion, and reviewed the manuscript. S.L.E. and M.T. researched data, edited and reviewed the manuscript, contributed to discussion, and performed all data analyses. S.L.E. and M.T. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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