

RESEARCH LETTER

When Metformin Fails in Type 2 Diabetes Mellitus

Type 2 diabetes mellitus is a complex and progressive disease that shows an apparently unstoppable increase worldwide. The last report on health in the United States in 2009 shows that 15% or more of the adult population 65 years and older is taking antidiabetic drugs, with an absolute increase of 6% compared with the years 1988 through 1994.¹ Moreover, diabetes is the third cause of death for women and the fourth for men.² Tight glycemic control, to maintain a hemoglobin A_{1c} (HbA_{1c}) concentration of 7% or lower, is recommended for all nonpregnant adults with diabetes to minimize the risk of long-term vascular complications.³ As a consequence, current diabetes guidelines⁴ suggest adjustment of therapy based on HbA_{1c} level. The American Diabetes Association/European Association for Study of Diabetes (ADA/EASD) guidelines indicate metformin as starter pharmacological therapy in drug-naive patients with type 2 diabetes (step 1) and then insulin (basal) or a sulfonylurea when metformin fails (step 2).⁴ All other glucose level-lowering therapies are only recommended for selected clinical settings. In theory, the posttreatment HbA_{1c} status (<7% vs ≥7%) should condition any future therapeutic choice; however, we cannot find any study that systematically assessed the pro-

portion of patients with type 2 diabetes reaching the HbA_{1c} target of 7% with antidiabetic drugs after metformin treatment failure.

Methods. We performed an electronic search via MEDLINE through June 2010 for randomized controlled trials (RCTs) evaluating insulin and noninsulin antidiabetic drugs added to metformin treatment in patients with type 2 diabetes not adequately controlled with maximal tolerated doses of metformin. Randomized controlled trials were included if they were parallel-design trials, treated patients for at least 12 weeks, and reported HbA_{1c} outcomes. We transformed the proportions of patients achieving the target (HbA_{1c} level <7%) into a quantity suitable for the usual fixed and random effects summaries (the Freeman-Tukey variant of the arcsine square root transformed proportion). The pooled proportion was calculated as back-transformation of the weighted mean of the transformed proportions, using DerSimonian-Laird weights⁵ for the random effects model. In 9 of the 30 RCTs that did not report the proportion of patients at the target level, we used an algorithm that was a linear regression model relating the logit of the proportion at target HbA_{1c} level $\{\log[p/(1-p)]\}$ at the end of the treatment:

$$\log(p/1-p) = 11.68167 - 164.3119 \times \text{HbA}_{1c} - \text{end.}$$

This equation explained the 88% variability between studies.

Results. We used the ADA/EASD algorithm for medical management of hyperglycemia in type 2 diabetes: well-

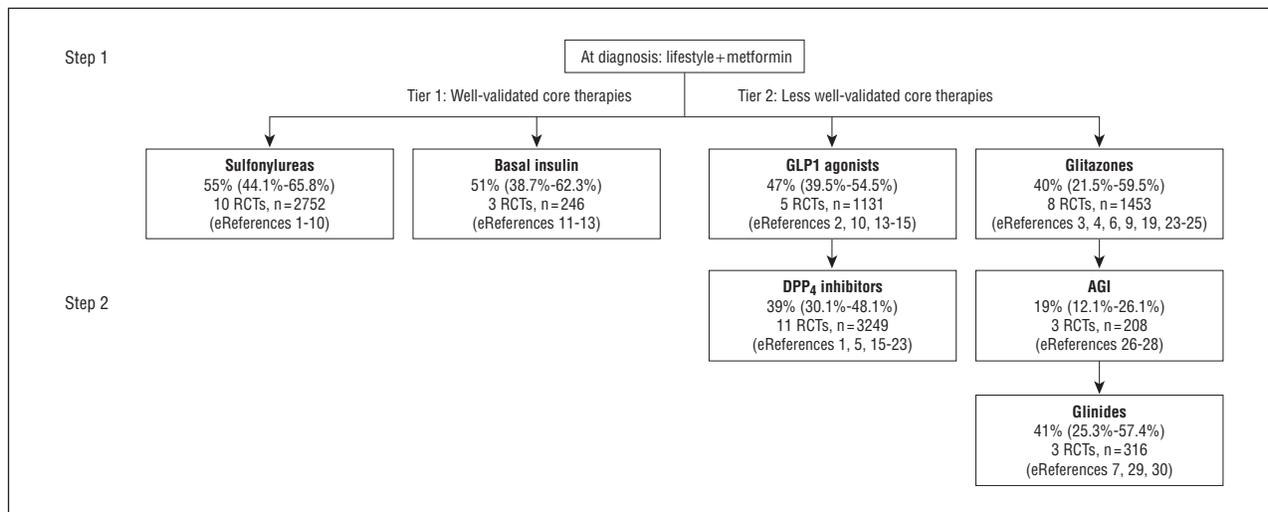


Figure. Percentage of patients with type 2 diabetes achieving the American Diabetes Association hemoglobin A_{1c} (HbA_{1c}) target of lower than 7% after failure with metformin monotherapy. Data are presented as pooled proportion and 95% confidence interval. Sulfonylureas included glimepiride, gliclazide, glipizide, and glyburide; basal insulin included insulin glargine; GLP1 agonists included exenatide and liraglutide; DPP4 inhibitors included sitagliptin, vildagliptin, alogliptin, and saxagliptin; glitazones included rosiglitazone and pioglitazone; AGI (α-glucosidase inhibitors) included acarbose and miglitol; and glinides included nateglinide and repaglinide. The number of randomized controlled trials (RCTs) and total patients, with the Web references (eReferences; <http://www.archinternmed.com>), are reported in each box.

validated core therapies (sulfonylureas or basal insulin) and less well-validated therapies, including all other non-insulin drugs. The results are reported in the **Figure**. In quantitative absolute terms, sulfonylureas and basal insulins in the well-validated tier obtain the best results, while GLP-1 agonists in the less well-validated tier had the higher proportion of patients at the target level. The proportions of patients attaining the HbA_{1c} target of <7% with other drugs ranged from 19% with α -glucosidase inhibitors to 41% with glinides. All results were characterized by a wide confidence interval.

Comment. Approximately one-half or more of patients with type 2 diabetes did not obtain an HbA_{1c} level lower than 7% in any further step after metformin treatment failure. The descriptive nature of our analysis does not allow a comparative evaluation. However, previous detailed meta-analyses⁶ have indicated that all noninsulin antidiabetic drugs have similar effects on HbA_{1c} levels. This also seems consistent with our results, since the wide confidence interval made most drugs fairly similar. It seems unlikely that future studies will improve these percentages substantially, unless therapeutic inertia (the health care provider's failure to increase therapy when the treatment goals are unmet) is bypassed. Most recent RCTs recruited patients with type 2 diabetes with a mean HbA_{1c} level of approximately 8.5%: this may favor a greater absolute HbA_{1c} decrease,⁷ but is associated with a lower percentage of patients achieving the ADA HbA_{1c} level target of <7%. A recent retrospective study of 48 000 diabetic patients in the real world suggests that an HbA_{1c} value of 7.5% is associated with the lowest death rate and lowest rate for large vessel disease.⁸ One action could be to increase the target in order to have more patients at goal with the best outcomes: our preliminary data indicate that this action would result in approximately two-thirds of patients with type 2 diabetes on intensified insulin regimens achieving the goal of 7.5% for HbA_{1c}, vs approximately 54% (95% CI, 43.5%-64.0%) on the actual target (\leq 7%). Hopefully, this strategy would not only lead to a cosmetic effect (more patients at goal) but also limit the risk associated with lower targets (<7% or <6.5%). We need more help from those involved in writing guidelines to walk the fine line between searching for a wiser and safer HbA_{1c} goal and minimizing the harms of any treatment.

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script: Esposito and Giugliano. *Critical revision of the manuscript for important intellectual content:* Bellastella. *Statistical analysis:* Giugliano. *Administrative, technical, and material support:* Esposito and Bellastella. *Study supervision:* Esposito.

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COMMENTS AND OPINIONS

HEALTH CARE REFORM

Caution in Generalizing Part D Results to Medicare Population

In the August 9/23, 2010, issue, Millett and colleagues^{1(p1327)} wrote,

Mean out-of-pocket annual expenditures on all medications decreased by 32% . . . from \$1011 to \$691, in the year after Medicare Part D was implemented compared with the year before in all Medicare beneficiaries participating in the M[edical] E[xpenditure] P[anel] S[urvey].

This result is 2 to 3 times larger than any result reported among at least 4 previous Part D evaluations (ranging from 13%-18%).²⁻⁵ Millett and colleagues acknowledge the difference but suggest that the prior studies all underestimated the benefits of Part D.

There may be another reason for the anomalous findings. The investigators excluded a large proportion (approximately 60%) of the original 2005 elderly and Medicare-eligible MEPS sample in order to use a longitudinal study design. Such a large exclusion can significantly and systematically diminish the generalizability of the re-