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. Moreover, diabetes is the third cause of death for women and the fourth for men. Tight glycemic control, to maintain a hemoglobin A1c (HbA1c) concentration of 7% or lower, is recommended for all nonpregnant adults with diabetes to minimize the risk of long-term vascular complications. As a consequence, current diabetes guidelines suggest adjustment of therapy based on HbA1c 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). All other glucose level–lowering therapies are only recommended for selected clinical settings. In theory, the posttreatment HbA1c status (<7% vs ≥7%) should condition any future therapeutic choice; however, we cannot find any study that systematically assessed the proportion of patients with type 2 diabetes reaching the HbA1c 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 (RTCs) 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 HbA1c outcomes. We transformed the proportions of patients achieving the target (HbA1c 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 backtransformation of the weighted mean of the transformed proportions, using DerSimonian-Laird weights for the random effects model. In 9 of the 30 RTCs 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 HbA1c level {log[p/(1−p)]} at the end of the treatment:

$$\log(p/1-p) = 11.68167 - 164.3119 \times \text{HbA1c-end}.$$  

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](https://www.archinternmed.com/content/171/4/365.full.png)

**Figure.** Percentage of patients with type 2 diabetes achieving the American Diabetes Association hemoglobin A1c (HbA1c) 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 HbA1c 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 HbA1c 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-analyses have indicated that all noninsulin antidiabetic drugs have similar effects on HbA1c 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 HbA1c level of approximately 8.5%; this may favor a greater absolute HbA1c decrease, but is associated with a lower percentage of patients achieving the ADA HbA1c level target of <7%. A recent retrospective study of 48,000 diabetic patients in the real world suggests that an HbA1c value of 7.5% is associated with the lowest death rate and lowest rate for large vessel disease. The percentage of patients achieving the ADA HbA1c level target of approximately 8.5%: this may favor a greater absolute HbA1c decrease, but is associated with a lower percentage of patients achieving the ADA HbA1c level target of <7%. A recent retrospective study of 48,000 diabetic patients in the real world suggests that an HbA1c 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 HbA1c, vs approximately 54% (95% CI, 43.5%-64.0%) on the actual target (≤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 HbA1c goal and minimizing the harms of any treatment.

**Katherine Esposito, MD, PhD**  
**Giuseppe Bellastella, MD**  
**Dario Giugliano, MD, PhD**  

Author Affiliations: Department of Geriatrics and Metabolic Diseases, Second University of Naples, Naples, Italy.  
**Correspondence:** Dr Giugliano, Department of Geriatrics and Metabolic Diseases, Second University of Naples, Piazza L. Miraglia, 80138 Naples, Italy (dario.giugliano@unina2.it).

Author Contributions: Dr Giugliano had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.  
**Study concept and design:** Esposito and Giugliano.  
**Acquisition of data:** Bellastella and Giugliano.  
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**Drafting of the manuscript:** Esposito and Giugliano.  
**Critical revision of the manuscript for important intellectual content:** Bellastella.  
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