VU Research Portal

Glycemic Control and Complications in Type-2 Diabetes

van der Does, F.E.E.; Bouter, L.M.; Heine, R.J.

published in
Diabetes Care
1993

DOI (link to publisher)
[10.2337/diacare.16.6.952a](https://doi.org/10.2337/diacare.16.6.952a)

document version
Publisher's PDF, also known as Version of record

[Link to publication in VU Research Portal](#)

citation for published version (APA)
van der Does, F. E. E., Bouter, L. M., & Heine, R. J. (1993). Glycemic Control and Complications in Type-2 Diabetes. *Diabetes Care*, 16(6), 952-952. <https://doi.org/10.2337/diacare.16.6.952a>

General rights

Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the public portal ?

Take down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

E-mail address:
vuresearchportal.ub@vu.nl

Glycemic Control and Complications in Type II Diabetes

In our opinion, the objectives of both the feasibility trial and the study that is intended to ensue from it, as presented by Dr. Abaira et al. (VA CS Group) (1), are highly relevant. If it is possible to achieve and maintain a statistically significant difference in HbA_{1c} between two otherwise comparable groups—within the acceptable range of glycemic values, that is—we can finally address the ultimate question of what target level of glycemic control can best be strived for in type II diabetes.

In 1989, our research group (the Hoorn Study) planned a very similar feasibility study, which is currently in the recruitment phase. Just as the VA CS Group, we also had concerns about the difference in intensity of care between the two treatment arms, possibly leading to a different degree of unintended effects in both arms during follow-up, which cannot always be measured precisely nor attributed to the level of glycemic control. If, during follow-up, a difference in both HbA_{1c} and, e.g., lipid levels or blood pressure should develop, we would not be able to ascertain whether the changes in these other risk factors would be attributable to glycemic level alone or partly to unintended differences in, e.g., dietary habits or physical fitness. So, if the main aim is to investigate the effect of glycemic control per se on macrovascular end points, it is necessary to make sure that any difference between the two groups after follow-up is attributable to the difference in level of glycemic control alone. As it is not feasible to mask determinant categories for both diabetes care professionals and patients, we are convinced that this problem cannot be fully overcome.

The second problem to be addressed arises from the comparison of a well-defined intensive treatment strategy with a less-defined standard treatment

that could change over time (not only in the course of the feasibility study, but also during an ensuing long-term trial). If a significant difference is established at one year, this does not guarantee maintenance of the difference over a longer period of time. For this to occur, a firm grip on both treatment arms is required. On one hand, it is pivotal to prevent so-called contamination, as it reduces the differences between the level of glycemic control in the groups: one may expect that the results of the standard treatment gradually come closer to those of the intensive treatment. On the other hand, it cannot be excluded that glycemic control during standard treatment would not be good enough to reach even acceptable levels. In this latter case, the real question—which level of glycemic control is necessary to prevent complications—cannot be answered. Both scenarios illustrate the necessity of having strict control over both arms of the study.

As a consequence of our view concerning these two potential problems, we have chosen a study design that differs from that of the VA CS Group on the following points: All participating type II diabetic patients are treated by their own general practitioner according to the same standardized step-up regimen, in collaboration with a diabetes educator and our research center, where facilities for education and consultation are provided. After baseline measurements, patients are randomly assigned to two (equally intensive) treatment groups: the only contrast between these groups being the target values of glycemic control, which are a fasting capillary blood glucose level ≤ 6 mM or a fasting glucose ≤ 8 mM (rounded numbers) for the intensive and standard groups, respectively. Participating general practitioners are asked to implement the next treatment step if the target has not been reached yet, and to refrain from taking any steps as soon as the assigned target values are reached. In theory, this design creates two equally well-defined, intensively treated groups, with the only dif-

ference being the glycemic values, both within the acceptable range.

In conclusion, we think it is essential in studies like these to ensure that the degree of attention and education provided to the patients in the compared groups is fully similar, in order to provide a clear answer to an extremely important question.

FERDINAND E.E. VAN DER DOES, MD
LEX M. BOUTER, PHD
ROBERT J. HEINE MD, PHD

FROM THE INSTITUTE FOR RESEARCH IN EXTRAMURAL MEDICINE, VRIJE UNIVERSITEIT AMSTERDAM, THE NETHERLANDS.

ADDRESS CORRESPONDENCE TO FERDINAND E.E. VAN DER DOES, MD, INSTITUTE FOR RESEARCH IN EXTRAMURAL MEDICINE, VRIJE UNIVERSITEIT AMSTERDAM, VAN DER BOECHORSTSTRAAT 7, 1081 BT AMSTERDAM, THE NETHERLANDS.

VA CS, VETERANS AFFAIRS COOPERATIVE STUDY; TYPE II DIABETES, NON-INSULIN-DEPENDENT DIABETES MELLITUS.

References

1. Abaira C, Emanuele N, Colwell J, Henderson W, Comstock J, Levin S, Nuttall F, Sawin C. VA CS Group: Glycemic control and complications in type II diabetes: design of a feasibility trial. *Diabetes Care* 15: 1560-71, 1992

Response to Van der Does et al.

We appreciate the interest and comments of Dr. Van der Does et al. We, too, are concerned that the two randomized groups must be the same in all respects except for the level of glycemic control. Our trial has been carefully designed to prevent unintended effects of risk factors between arms by defining identical patient education and treatments for these risk factors in both treatment groups. Should unexpected differences appear, these risk fac-

tors will be included as covariates in the statistical analysis of results. In the long-term trial, we will further attempt to prevent imbalances by having both groups of patients seen in the clinic every 6 wk.

The second problem mentioned by Dr. Van der Does is already partially answered in the preliminary report of the results of the feasibility trial, which shows that the control group retains the prevalent fasting glycemic level of the full cohort at entry, 12 mM, which is similar to outpatient assessments both here and in Europe (1,2). By contrast, the mean fasting glycemia in the intensive group is 6 mM, whereas the level of separation between groups remains consistent for >2 yr of follow-up (1). These levels are similar to those reported for several years in the DCCT (3). We believe it is highly unlikely that the HbA_{1c} values in the standard group will drift significantly toward the intensively treated group. Our trial is monitored by an independent data monitoring board. Should a satisfactory HbA_{1c} separation not be maintained between the two treatment groups, mechanisms exist in the CS program to stop the trial.

It would appear that by design, the Hoorn Study aims at a narrow level of glycemic separation, not unlike those obtained in the different intervention arms in the UKPDS (4). These European studies in type II diabetes, and the VA CSDM, will likely complement each other. If glycemic regulation is effective in preventing macrovascular events, it will be important to determine the desired level of HbA_{1c} . By choosing two intensive levels of glycemic regulation, the Hoorn Study may help determine this level. On the other hand, if glycemic regulation is important, the macrovascular event rates in these two intensive arms may be similar. In this case, a very large sample size may be required for meaningful results to emerge.

CARLOS ABRAIRA, MD
JOHN COLWELL, MD, PHD
WILLIAM HENDERSON, PHD
VA CS GROUP (CSDM)

FROM THE DEPARTMENT OF VETERANS AFFAIRS, EDWARD HINES, JR. HOSPITAL, HINES, ILLINOIS.

ADDRESS CORRESPONDENCE TO CARLOS ABRAIRA, MD, DEPARTMENT OF VETERANS AFFAIRS, EDWARD HINES, JR. HOSPITAL (151Y), RESEARCH SERVICE, ROOM 1B217, HINES, IL 60141.

DCCT, DIABETES CONTROL AND COMPLICATIONS TRIAL; CS, COOPERATIVE STUDY; UKPDS, UK PROSPECTIVE DIABETES STUDY; TYPE II DIABETES, NON-INSULIN-DEPENDENT DIABETES MELLITUS; VA CSDM, VETERANS AFFAIRS COOPERATIVE STUDY ON CONTROL AND COMPLICATIONS IN DIABETES MELLITUS TYPE II.

References

1. Abraira C, Johnson N, Colwell J, and the VA CSDM Group. A successful feasibility trial: The VA Cooperative Study on Control and Complications in Diabetes Mellitus Type II (CSDM) (Abstract). *Diabetes* 42 (Suppl. 1):147A, 1993
2. Abraira C, Emanuele N, Colwell J, Henderson W, Comstock J, Levin S, Nuttall F, Sawin C. VA Cooperative Study Group (CSDM). Glycemic control and complications in type II diabetes: design of a feasibility trial. *Diabetes Care* 15:1560-71, 1992
3. DCCT Research Group. Diabetes Control and Complications Trial (DCCT) update. *Diabetes Care* 13:427-33, 1990
4. UK Prospective Diabetes Study Group. UK Prospective Diabetes Study (UKPDS). VIII. Study design, progress, and performance. *Diabetologia* 34:877-90, 1991