Impact of a randomized control group on perceived effectiveness of a Disease Management Programme for diabetes type 2

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Background: Disease Management Programmes (DMPs) are proposed to enhance the quality of care, to improve health outcomes and to reduce costs. Yet, the evidence regarding the effectiveness of such structured approaches remains uncertain. Randomized controlled trials (RCTs) represent the gold standard of evaluation for complex interventions. However, most of the evidence derives from non-randomized or even uncontrolled trials. We therefore tried to assess the impact of a randomized control group on the interpretation of DMP effectiveness.

Methods: We analyzed the data of a RCT on a DMP for diabetes type 2 by creating two scenarios. The first solely includes data of the intervention group (n = 649), representing an ‘uncontrolled pre-test–post-test analysis’. The second comprehends all data (n = 1489) of the ‘randomized controlled analysis’. HbA1c was used as the primary outcome measure for metabolic control in diabetes. Depending on either scenario, we calculated relative and absolute risk reduction regarding clinically relevant endpoints and estimated costs by extrapolating our results according to the UK Prospective Diabetes Study (UKPDS) findings. Results: The HbA1c reduction attributed to the DMP was 0.41% (uncontrolled analysis) vs. 0.13% (controlled comparison). Estimations of relative risk reduction for cardiovascular disease were 4.6% vs. 1.4%. The estimated numbers needed to treat (NNT) to avoid one myocardial infarction within 10 years differed from 125 (uncontrolled analysis) to 417 patients (controlled comparison), which led to a substantial scenario-dependent difference in cost estimations. Conclusion: Uncontrolled pre-test–post-test evaluation might lead to crucial overestimation of DMP effectiveness. We therefore recommend randomized controlled evaluations prior to long-term implementation.

Introduction

Chronic diseases are on the rise and will result in major challenges for health-care systems in the 21st century. The prevalence of diabetes mellitus type 2 is increasing worldwide for all age groups due to population growth, ageing, urbanization, obesity and physical inactivity. In Austria, at least 300,000–315,000 patients suffer from diabetes type 2, which corresponds to 4.2–4.6% of the adult population. Several studies have shown deficits in the implementation of standard care for diabetes type 2 in Austria and there is demand for management optimization.

The high prevalence of diabetes mellitus type 2 and the deficits in care prompted the development of Disease Management Programmes (DMPs) such as the Austrian DMP ‘Therapie Aktiv’. However, published evidence on the effectiveness of such DMPs is inconsistent and inconclusive. A systematic review of diabetes mellitus programmes led to the conclusion that DMPs may hold the potential to better long-term outcome due to improvements in glycemic control, but the validity of this review is limited due to the inclusion of non-randomized studies and a significant heterogeneity among studies. Another systematic review also reporting a mean HbA1c reduction of ~0.5% even included all study types (e.g. non-controlled observational studies).

Most of the evidence regarding effectiveness of DMPs derives from uncontrolled pre-test–post-test studies, even though randomized controlled trials (RCTs) have been described as the best method for assessing a causal relationship between a complex intervention (such as a DMP) and clinical outcomes. So far, only few randomized controlled studies that analyzed the outcome of a DMP programme have been published. Our study represents the first randomized controlled evaluation trial of a DMP implemented by public health insurance in Europe. Although the randomized controlled approach has been deemed essential, it has never been accomplished in Germany (where some of the world’s largest programmes have been launched by statutory public health insurance since 2002).

To emphasize the importance of the randomized controlled approach in the evaluation of complex interventions like DMPs, we investigated in this study the discrepancy between a randomized controlled vs. uncontrolled evaluation design regarding the interpretation of DMP effectiveness.

A fundamental aim in health care is to gain clinically relevant benefits for patients. Hence, it is important to translate methodologically sound and statistically significant research into clinically relevant recommendations and guidelines. Not every statistically significant result is clinically relevant. Thus a small HbA1c improvement may be statistically significant in a trial with a sufficiently large number of participants, but it may not be relevant regarding clinical outcome, as the principal objective of HbA1c reduction is the prevention of cardiovascular complications.

The risk for cardiovascular disease is considerably higher in diabetic patients than in non-diabetic patients. The risk for myocardial infarction (MI) in diabetic patients without prior MI may be as high as the risk for re-infarction in non-diabetic patients. Overall, diabetic patients experience very high mortality especially from cardiovascular disease, compared with the general population. We therefore used extrapolated cardiovascular outcome in this study to show the clinically relevant effects of a DMP depending on the evaluation method.

To demonstrate the possible impact of a randomized control group on the interpretation of DMP effectiveness, we re-analyzed the data of our RCT evaluating the effectiveness of the Austrian DMP ‘Therapie Aktiv’ for diabetes type 2. The programme was designed and implemented by statutory public health insurance, and physicians as well as patients were asked to participate on a voluntary basis. We created two scenarios by including and alternatively excluding data of the control...
group. One scenario is representing an uncontrolled pre-test–post-test analysis of enrolled patients, like most of the published DMP evaluations have been carried out, and the other one includes the randomized controlled comparison. Based on the respective results regarding reduction in the primary outcome measure HbA1c, we interpreted the respective programme effectiveness regarding clinically relevant outcomes for each group.

**Objectives**

This work focuses on the impact of a randomized control group on the interpretation of effectiveness of a DMP for diabetes type 2. HbA1c is used as the primary measure of metabolic control. Our principal research question is, how the control group modifies the perceived effectiveness of the DMP regarding (i) improvement in metabolic control, (ii) relative risk reduction (RRR) of clinically relevant endpoints and (iii) estimated costs.

**Methods**

This work is based on the results of a pragmatic cluster-randomized controlled superiority trial (RCT) of the DMP ‘Therapie Aktiv’ with an observation time of 1 year. The RCT has been approved by the ethics committee of Salzburg, Austria, and has been registered with Current Controlled Trials Ltd. (ISRCTN27414162) on 12 July 2007. Details of the methodology and study protocol have been published previously,15 and the main results of the RCT also have been published.11

**Summary of RCT design and participants**

Cluster randomization of the RCT was carried out at the district level of the Salzburg province that resulted in a three-level cluster design in which the surgery was nested within the district, and patients were nested within the surgeries. The RCT took place in the province of Salzburg with a total population of about 500 000. The estimated prevalence of diabetes type 2 is ~2.5–3% in Salzburg, which is slightly lower than the Austrian average. Participation in the study was offered to all 275 primary care physicians having a contract with the public health insurance. Ninety-two physicians (participation rate 33.5%) continuously recruited 1489 patients with diabetes type 2 for cluster randomization (649 intervention, 840 control).

**Description of the intervention DMP ‘Therapie Aktiv’**

The DMP includes the following components:

(i) a mandatory 10-h face to face training course for physicians, designed by the Austrian Diabetes Association (ÖDG), the Austrian Medical College (Ärztekammer) and the Austrian Society for General Practice (ÖGAM) consisting of an update in diabetes care, current guidelines of the ÖDG and practice management training;

(ii) nine hours of patient education in four modules with a group size of 3–12 patients. Patient education was organized by the Working Group for Preventive Medicine Salzburg (AVOS) using the ‘Düsseldorfer Modell’ curriculum;16,17

(iii) standardized documentation of physical examination, laboratory findings and diabetes complications in a DMP-form once a year;

(iv) structured interdisciplinary care according to the guidelines of the ÖDG;18 and

(v) agreement on therapeutic goals in a shared patient–physician decision-making process at 3-monthly intervals.

In the control group, physicians performed usual care. Usual care implies physical examination, laboratory tests and interdisciplinary care according to the respective physician rather than a structured protocol as defined within the DMP. Usual care might overlap with main elements of the DMP as guidelines of the ÖDG are valid countrywide and publicly available.

**Outcome measures and methods**

The primary endpoint of the RCT was the change in HbA1c from baseline to 12 months as the measure of metabolic control. Within this work, we used the primary outcome measure of our study to create two different scenarios to estimate the impact of the randomized control group.

(i) First scenario: we included data of the intervention group only, representing an uncontrolled pre-test–post-test analysis.

(ii) Second scenario: we included all data of the randomized controlled comparison (intervention and control group).

Secondly, we calculated the relative risk reduction (RRR) for cardiovascular disease by extrapolating and applying the results of a meta-analysis of the association between HbA1c and cardiovascular morbidity in diabetic patients19 to our study results. We thus calculated the possible RRR regarding cardiovascular events attributable to the DMP-induced HbA1c change in our study, assuming the HbA1c difference to stay the same as in our year of observation. We then estimated the absolute risk reduction (ARR) regarding cardiovascular events and diabetic complications by extrapolation of data from the UK Prospective Diabetes Study (UKPDS).20 as this study represents the best validated and well-documented long-term observation of a diabetic cohort. The calculated ARR enabled us to estimate the numbers needed to treat (NNT) within the DMP to avoid one MCI or one diabetes-related complication in 10 years. The NNT and the actual costs of the DMP were used to calculate the costs to avoid one MCI or one diabetes-related complication.

**Statistical methods**

All statistical analyses were performed with IBM® SPSS® Statistics18.0.

**Results**

The results of the RCT relating to the primary outcome measure are presented in tables 1 and 2. There was no significant difference regarding HbA1c at baseline.

After an average of 401 ± 47 days, 90.9% of the intervention group (590 patients) and 89.8% of the control group (754 patients) had complete data regarding primary outcome measure. Because of the realities of adherence and retention in a programme such as the DMP, we evaluated our data in an intention-to-treat (ITT) approach using the last available data carried forward method. We found a decrease in the HbA1c of 0.41% in the intervention group and a decrease of 0.28% in the control group. The pre–post-comparison was significant at a level of $P < 0.0001$ for both groups (table 2). The ITT between-group analysis demonstrated a small but significantly larger reduction of HbA1c in the intervention group ($-0.13\%$, $P = 0.026$) (table 2).

Selvin et al.19 performed a meta-analysis on glycosylated haemoglobin and cardiovascular disease in diabetes mellitus, which showed a relative risk (RR) for cardiovascular disease within diabetic patients of 0.9 (95% CI 0.85–0.95) for 0.9% points HbA1c decrease. Assuming a linear relationship, a RR of 0.9 is equal to a 10% RRR per 0.9% points HbA1c decrease. In the uncontrolled pre-test–post-test comparison (intervention group only), the HbA1c decrease was 0.41. We calculated the RRR as follows: if a 0.9% HbA1c-reduction results in a 10% RRR, then a 0.41% HbA1c reduction will produce a 10*0.41/0.9% = 4.6% RRR. Accordingly, RRR can be calculated for the net effect of the DMP, which is a HbA1c decrease.

**Table 1 Baseline data**

<table>
<thead>
<tr>
<th></th>
<th>Intervention</th>
<th>Control</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients at baseline</td>
<td>649</td>
<td>840</td>
<td>0.43*</td>
</tr>
<tr>
<td>Percentage of women</td>
<td>49.0</td>
<td>46.9</td>
<td></td>
</tr>
<tr>
<td>Age (years ± SD)</td>
<td>65.4 ± 10.4</td>
<td>65.5 ± 10.4</td>
<td>0.95*</td>
</tr>
<tr>
<td>HbA1c (% ± SD)</td>
<td>7.46 ± 1.53</td>
<td>7.34 ± 1.31</td>
<td>0.10*</td>
</tr>
</tbody>
</table>

a: Fisher’s exact test
b: Independent t-test
Randomized controlled comparison

ARR (DMP) = 17.4*1.4/100 = 0.24%. Hence, the NNT within the DMP to avoid one MCI in 10 years is 417 patients (100/0.24 = 417).

Accordingly, we calculated the ARR for any diabetes-related complication based on the AR of 46% for any diabetes-related event in the UKPDS and the estimation of RRR for any diabetes complication derived from the UKPDS. The effects of the DMP for uncontrolled vs. randomized controlled comparison regarding ARR and NNT are depicted in table 3.

Knowing the NNTs enable us to estimate the costs of the DMP to avoid diabetes-related complications.

Public health insurance reimburses the DMP physicians with 52 € for the initial DMP examination and 26 € for one DMP follow-up examination every 3 months. This adds up to 52 € + 3*26 € + 9*4*26 € = 1066 € of DMP-costs/patient in 10 years.

Uncontrolled pre-test–post-test comparison

NNT for 10 years within the DMP programme is 125 patients to avoid one MCI, respectively, 47 patients to avoid one diabetes-related complication. Hence, the resulting DMP-related costs are 1066*125 = 133 250 € to avoid one MCI within the next 10 years, respectively, 1066 * 43 = 45 838 € to avoid any diabetes-related complication.

Randomized controlled comparison

Based on the NNTs, estimated within the randomized controlled comparison, the DMP-related costs to avoid one MCI, respectively, any diabetes-related complication within the next 10 years add up to 1066*417 = 444 522 € and 1066*135 = 143 910 €, respectively.

The estimated costs by the DMP to avoid one MCI (one diabetes-related complication) differ more than 300 000 €, and almost 100 000 € to avoid any diabetes-related complication, depending on which scenario the calculations are based on. The graphic presentation of cost estimations based on the two different scenarios is depicted in figure 1.

Discussion

The two different evaluation scenarios of the DMP (uncontrolled pre-test–post-test analysis vs. randomized controlled analysis) led to quite different results regarding interpretation of effectiveness. When data from the control group was not included, we found a >3-fold over-estimation of HbA1c reduction resulting in an overestimation of risk reduction of > 200% for clinically relevant outcomes such as cardiovascular events.

As most of the published information regarding DMP effectiveness derives from uncontrolled studies, the validity of the evidence must thoroughly be scrutinized. The uncontrolled pre-test–post-test comparison remains a weak evaluation method. Measured gross effects might be due to multi-causal reasons, most notably regression to the mean, study effects or ‘participation effect’ as well as other external confounding factors such as ageing or natural course of disease. This implies that both internal and external validity are rather limited in any uncontrolled pre-test–post-test scenario. Positive results derived from
such studies must, therefore, be considered with caution and may not be
generalizable (external validity), while randomized controlled compar-
sions are characterized by a high-internal validity. With regard to gener-
alizability, results can be transferred to a similar setting, i.e. in our case a
DMP implemented and carried out on a voluntary basis with highly
motivated physicians.

DMPs are cost-intensive interventions and induce considerable
additional workload for health-care providers. Therefore, programmes
should be evaluated thoroughly before widespread implementation. The
opportunity of a randomized controlled evaluation of a DMP with more
than 2 million enrolled patients (2005) was missed in Germany, which
was highly criticized. The authors summarized several rationales to
emphasize the need for randomized controlled evaluations of DMPs. due
to various types of bias only a randomized controlled study design is
considered adequate to prove the effectiveness of a complex intervention
like a DMP. Methodologically sound evaluation studies are indispensable
to enable international comparison of evidence. In a recent publication,
referring to disease management evaluation in Germany, Schafer and
colleagues came to the conclusion that selection bias may impair the
assessment of differences in outcome quality between enrolled and
usual-care patients. As self-active and motivated patients with a lower
risk for diabetic complications and overall morbidity seem to be more
likely enrolled in the German DMP, selection effects may account for
better outcomes (such as reduction in mortality) within the
non-randomized evaluation trials of the DMP for type 2 diabetes.

As described by Campbell et al., the randomized controlled
evaluation might be embedded within a multi-phase evaluation model.
Such integration of formative and summative evaluation strategies as
recommended by Campbell appears to be a promising method for
sound evaluation of DMPs.

**Limitations**

Regarding the extrapolation on DMP-related costs, we neglected the
programme development and evaluation expenses as well as costs
induced by DMP-related diagnostic measures and medication, because
we wanted to focus on direct DMP costs. The results of our economic
analysis can therefore not be interpreted as absolute numbers but rather
as a trend illustrating the potential economic misinterpretation within an
uncontrolled evaluation. Detailed assessment of return on investment and
cost-effectiveness of a DMP requires further analysis and comparison of
DMP-related costs to determine the savings achieved by the avoidance of
myocardial infarctions and other diabetes-related complications.

**Conclusion**

The results of our study show, that an uncontrolled pre-test–post-test
evaluation of the DMP ‘Therapie Aktiv’ for diabetes mellitus type 2 might
lead to a crucial overestimation of effectiveness and cost effectiveness of
this intervention. As DMPs are in the majority of cases large scale, costly
and work-intensive public health interventions, we recommend a
randomized controlled evaluation prior to widespread implementation
of such programmes.

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University, Salzburg.

**Conflicts of interest:** None declared.

**Key points**

- Uncontrolled pre-test–post-test evaluation of DMPs might lead
to overestimation of effectiveness.
- In consequence this might substantially skew cost estimations.
- DMPs are costly and work-intensive public health interventions
and therefore should be evaluated within a RCT prior to
widespread implementation.

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Figure 1 Estimated costs based on uncontrolled pre-test–post-test vs. randomized controlled comparison
Effect of physician collaboration network on hospitalization cost and readmission rate

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Background: Previous studies have documented the effect of collaboration among physicians on the effectiveness in delivering health services and in producing better patient outcomes. However, there is no systematic empirical study suggesting the underlying relationship between the collaboration network of physicians and its effect on hospitalization cost and readmission rate. In this study, we explore the effect of different attributes (i.e. degree centrality, betweenness centrality, network density and network distance) of physician collaboration network (PCN) on hospitalization cost and readmission rate. Method: We analyse health insurance claim data set of total hip replacement (THR) patients to construct PCN and to test the effect of its network attributes on hospitalization cost and readmission rate. We consider patient age as moderating factor, which could affect the relation of the PCN attributes with hospitalization cost and readmission rate. Results: We find that degree centrality (i.e. level of involvement) and network density (i.e. level of connectedness) of PCN are negatively correlated with hospitalization cost and readmission rate. In contrast, betweenness centrality (i.e. capacity to control the flow of information) is found positively correlated with hospitalization cost and readmission rate. Conclusion: The results show that the structure of PCNs is related to indicators of hospital costs and quality (readmission). In their respective hospitals, health-care managers or administrators may follow our research findings to reduce cost and improve quality.

References: