Improving an Adherent-Patient Subgroup Analysis of the Diabetes Prevention Program and Outcomes Study

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Introduction/Objectives

In 2013, Herman et al[1] published an adherent-patient subgroup (APS) cost-effectiveness analysis (CEA) of the 10-year Diabetes Prevention Program and DPP Outcomes Study (DPP/DPPOS), concluding lifestyle modification (LS) and metformin (MET) were cost-effective compared with placebo (PBO) for adherent patients.

Several concerns limit the relevance of that analysis: Incremental cost-effectiveness ratios (ICERs) were not calculated sequentially, quality-adjusted life years (QALYs) were estimated using nonstandard methods, and the time horizon included years 4–10 during which treatment arms were contaminated, reducing any relevance to the randomized interventions. In addition, adherence definitions differed across arms, with PBO assumed to have 100% adherence despite evidence that only approximately 77% of PBO participants were adherent.[2]

We sought to revise the analysis using observed PBO adherence, an uncontaminated 3-year horizon, and conventional economic methods.

Methods

We reanalyzed the APS using the first 3 years of the DPP/DPPOS (pre-contamination). QALYs were calculated conventionally (average of beginning- and end-of-year utilities), rather than assigning end-of-year values to the full year as in Herman.[1] Costs and QALYs were evaluated from a healthcare system perspective and reported undiscounted for comparability with the original APS.

Placebo (PBO) adherence was modeled using observed prevalence (**0.77**) and relative risk of diabetes for adherent vs non-adherent participants (RR = **0.91**). The 3-year PBO diabetes incidence was **0.281**. This example is illustrative, not definitive.

Methods (cont.)

Expected outcomes for adherent PBO participants were reconstructed in two steps:

First, subgroup-specific diabetes risks were estimated by applying the relative risk to the ITT PBO diabetes incidence:

$$P(D)ADH = 0.91 \times P(D)nADH \quad \text{Eqn 1}$$

The observed PBO diabetes incidence must equal the weighted average of the two subgroup risks:

$$0.281 = 0.77 \times P(D)_{ADH} + 0.23 \times P(D)_{nADH} \quad \text{Eqn 2}$$

$$0.281 = 0.77 * (0.91 P(D)nADH) + 0.23 * P(D)nADH \quad \text{Eqn 3}$$

$$0.281 = P(D)nADH * (0.77 * 0.91 + 0.23*1) \quad \text{Eqn 4}$$

$$0.281 = 0.9307 * P(D)nADH \quad \text{Eqn 5}$$

$$P(D)_{nADH} = \frac{0.281}{0.9307} = \mathbf{0.302} \quad \text{Eqn 6}$$

$$P(D)_{ADH} = 0.91 * 0.302 = \mathbf{0.275} \quad \text{Eqn 7}$$

Second, costs and QALYs were modeled as functions of diabetes status (diabetes vs no diabetes), using diabetes-state costs and utilities from published DPP data.[3]

Expected costs and QALYs for adherent participants were then obtained by weighting diabetes-state outcomes by the corresponding subgroup-specific diabetes risks:

$$Q_{ADH} = P(ND)_{ADH} * Q_3^{ND} + P(D)_{ADH} * Q_3^{D}$$

$$C_{ADH} = \text{Inside Cost} + P(ND)_{ADH} * C_3^{ND} + P(D)_{ADH} * C_3^{D}$$

Interventions were ordered by effectiveness, and ICERs were calculated sequentially using standard incremental cost-effectiveness methods.

Results

Estimated revised adherent PBO outcomes were 2.0587 QALYs and $7,704, representing increases in both costs and QALYs relative to the Herman's estimates based on all PBO patients being treated as adherent (Table 1).

In the original 10-year APS, both LS and MET were cost-saving (less cost and greater QALYs) – when each was compared to PBO. Appropriate analysis of those data indicates that a more appropriate ICER comparing LS to MET shows LS as cost-effective (ICER < $15,000/QALY).

Our 3-year analysis using 100% adherence did not support any cost-savings claims (Table 1, row 1 vs. MET and LS). Appropriate ICER calculations for the original APS showed MET to be extendedly dominated, with the only decision-relevant ICER (LS vs. PBO) of $45,313 per QALY. MET is not cost-effective; LS is.

Using ***observed*** (<100%) PBO adherence, (Table 1, row 2), PBO QALYs are now higher than MET, altering the appropriate ICERs to be calculated. The 2 appropriate ICERs were: **PBO vs MET** ($33,225/QALY) and **LS vs PBO ($88,359/QALY).** LS is cost-effective (for WTP > $88,359).

Discussion/Conclusions

Adherent-patient subgroup (APS) analyses are sensitive to assumptions about adherence and require consistent definitions across treatment arms.

The assumption of 100% adherence in the placebo group is not supported by DPP data and biases estimated costs and QALYs.

Using observed adherence and a 3-year uncontaminated horizon, we reconstructed placebo outcomes for truly adherent participants. This resulted in higher estimated QALYs and costs for placebo.

The increase in QALYs was expected given lower diabetes risk among adherent participants, whereas the increase in costs was less anticipated, refined estimation methods may be needed.

Table 1: Original and Revised PBO 3-Year Costs and QALYs along with Unchanged MET and LS Values

Intervention	QALYs	Cost
PBO Original	2.0060	$ 5,867
PBO Revised	**2.0587**	**$ 7704**
MET	2.0125	$ 6,169
LS	2.0715	$ 8,835

Discussion/Conclusions (cont.)

When appropriate sequential ICER methods are applied, metformin is extendedly dominated, and lifestyle intervention remains the only cost-effective strategy under conventional thresholds. These findings demonstrate that correcting adherence assumptions and applying standard economic methods materially changes APS results and their interpretation.

However, elsewhere we argue (Poster EE222: QR below) that APS results, alone, provide no guidance for decision makers who generally can only imperfectly predict adherence. Additional decision-analytic frameworks and estimation of non-adherent outcomes are required to translate APS results into real-world policy decisions.

Our methods also enable estimation of outcomes for the previously unmodeled non-adherent PBO subgroup that can, with APS results and estimates of diagnostic accuracy, better inform decisions.

References

Poster EE222