Assessing the significance of HbA1c durability in cost effectiveness analysis of 2nd line oral therapies in the management of type 2 diabetes

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Introduction

Due to the progressive nature of type 2 diabetes mellitus (T2DM), patients generally require escalation of dose and/or the use of combination therapies in order to maintain acceptable levels of glycaemic control.

Time to therapy escalation is a function of both initial treatment effect and the long term ability to maintain HbA1c control (glycemic durability).

Modeling analyses commonly assume escalation to rescue therapy once the projected HbA1c time path exceeds a defined threshold level (Figure 1). Considering costs and efficacy of the selected rescue therapy, differences in glycemic durability may have considerable impact on time to treatment escalation and cost effectiveness.

Since most clinical trials are short term, glycemic long term durability is less well understood. Economic evaluations of diabetes interventions typically focus on the glucose lowering effect in the first year and glycemic durability is commonly assumed to be equal for treatment and comparator regimens.

For the extrapolation of HbA1c over time, long term studies are referenced although little information is available to inform glycemic durability for different interventions and/or treatment classes.

- The UKPDS study reported an overall 0.15 annual increase in HbA1c for patients treated with either sulfonylurea (SU) or insulin (1).
- The same study published a random effects model to extrapolate the time path of HbA1c (2).
- The ADOPT study (3) reported five year glycemic control for three different treatment classes (annual HbA1c increase of 0.13, 0.08 and 0.26 for patients treated with metformin, rosiglitazone and glyburide, respectively).

Objectives

The objective of this study was to assess the influence of differing rates of dual therapy failure when evaluating sulphonylurea compared to DPP-4s when added to metformin. In particular, to assess the levels of glycemic durability required to achieve DPP-4 cost effectiveness for willingness to pay thresholds of $US 100,000, 70,000 and 50,000.

Methods

This study used the IMS Core Diabetes Model (CDM), a validated and established diabetes model, to evaluate the cost effectiveness of metformin+ sulphonylurea (M+S) compared to metformin + DPP-4 (M+D).

Insulin rescue therapy (Ires) was applied to both arms at an HbA1c threshold of 7.5%.

Cost effectiveness analysis were conducted to explore ten alternative scenarios for glycemic durability:

The base case analysis assumed M+D and M+S had the same glycemic durability of 0.26% points annual increase in HbA1c.

Nine sensitivity analyses addressed improvement in durability favoring M+D applied in 10% increments (from 0.234 to 0.026 % annual increase).

HbA1c progression of insulin rescue therapy was determined by a random effects model based on UKPDS data (2).

Efficacy data for dual therapy was sourced from a published systematic review (4); HbA1c and BMI change of -0.8% and 0.199kg/m2 (M+D); -0.79% and 0.707kg/m2 (M+S) and -0.82 and 0.545 kg/m2 (Ires) respectively were applied (Table 1).

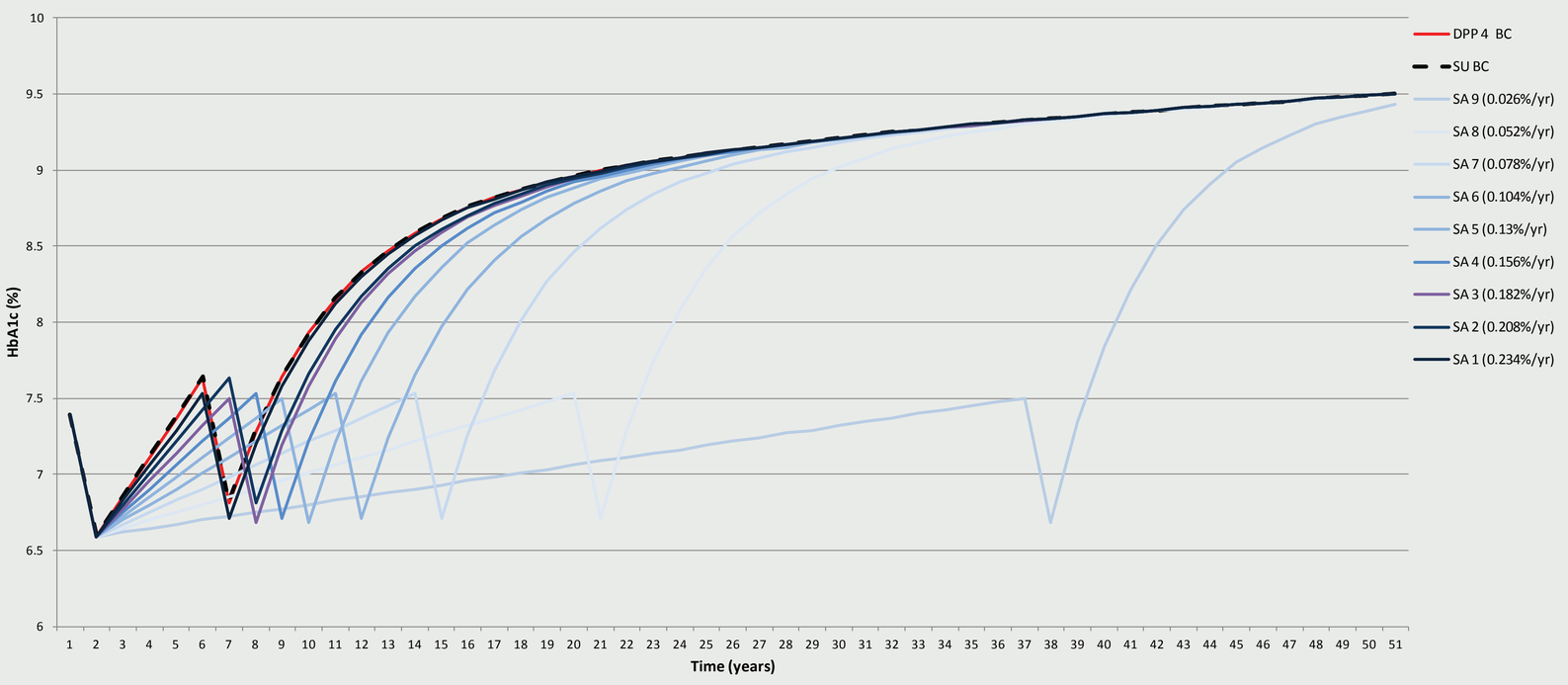
Hypoglycemia rates were obtained from a review conducted by Lund University to compare efficacy and safety of sulfonylureas versus DPP-4 inhibitors (5) (Table 1).

- Annual treatment costs were expected at $67.6 , $2520.0 and $1869.69 for (M+S), (M+D) and (Ires), respectively and based on wholesale acquisition cost (WAC) obtained from standard US list prices (2012) (Table 1).
- Lifetime analyses were conducted using NHANES cohort (6) to populate the patient characteristics in the modeling.
- Disutilities of -0.0052 (7) and -0.0038 (8) were applied to each symptomatic hypoglycemia event and 1 unit increase in BMI above 25 Kg/m2, respectively.
- Future benefits were discounted at 3%.

Table 1 – Efficacy and safety assumptions and treatment costs assumed for (M+S), (M+D) and (Ires)

	HbA1c (%)	BMI (kg/m2)	Severe Hypoglycemia (ev/100 pat yrs)	Symptomatic Hypoglycemia (ev/100 pat yrs)	Treatment costs ($ USD)
(M+S)	-0.79%	0.707	1.538	68.769	$67.6
(M+D)	-0.8%	0.199	0.1612	4.596	$2520.01
(Ires)	-0.82%	0.545	0	41.256	$1869.69

Figure 1) Glycemic durability patterns of MET+SU vs. MET+DPP4 for BC and 9 SA addressing improvement in durability in 10% increments (from 0.22 to 0.02 % annual HbA1c increase), followed by insulin rescue therapy.



Results

Predicted cost per quality adjusted life year (QALY) for M+S versus M+D ranged from $211,948 in the base case (BC) analysis (annual HbA1c increase of 0.26% per year) to $24,162 in SA 9 (annual HbA1c increase of 0.026%) (Figure 2).

In the BC analysis, mean time to therapy escalation was 5 years for (M+S). For (M+D) time to treatment escalation ranged from 5 years (BC) to 36 years in SA-9 (Figure 3).

As annual HbA1c increments were reduced from 90% to 10% for (M+D) alongside sensitivity analyses, the ICER declined in an approximately linear pattern from 88% to 11.4% (Figure 4).

Mean annual increments in HbA1c for M+D of 0.182%, 0.13% and 0.1% were necessary to achieve costs effectiveness at willingness to pay (WTP) thresholds of $100,000, $70,000 and $50,000 respectively.

Published HbA1c durability for M+D of 0.052% per year (9) was associated with a cost per QALY of $33,427 and predicted time to therapy escalation of approximately 15 years.

Figure 2) Predicted cost per quality adjusted life year (QALY) gained for M+S versus M+D

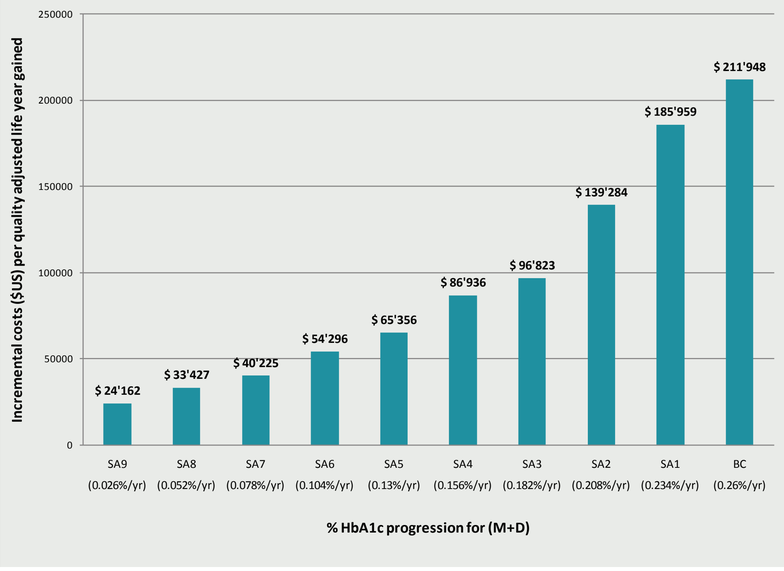


Figure 3) Average time to treatment escalation for M+S versus M+D

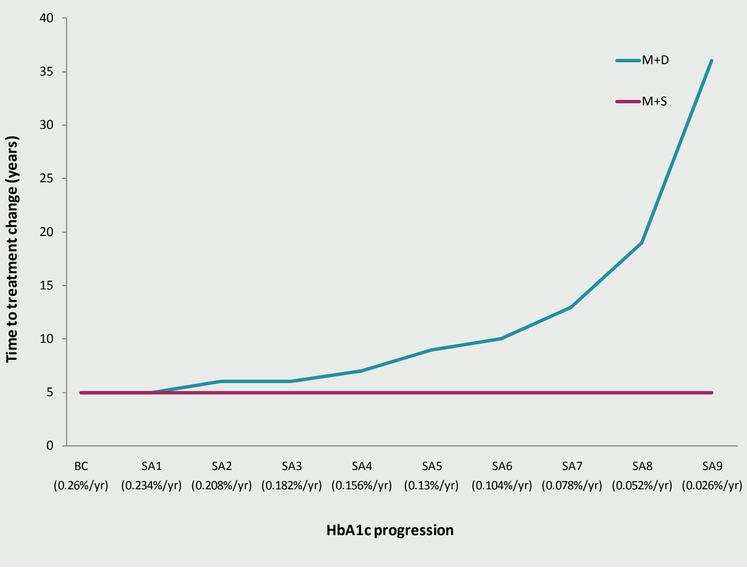
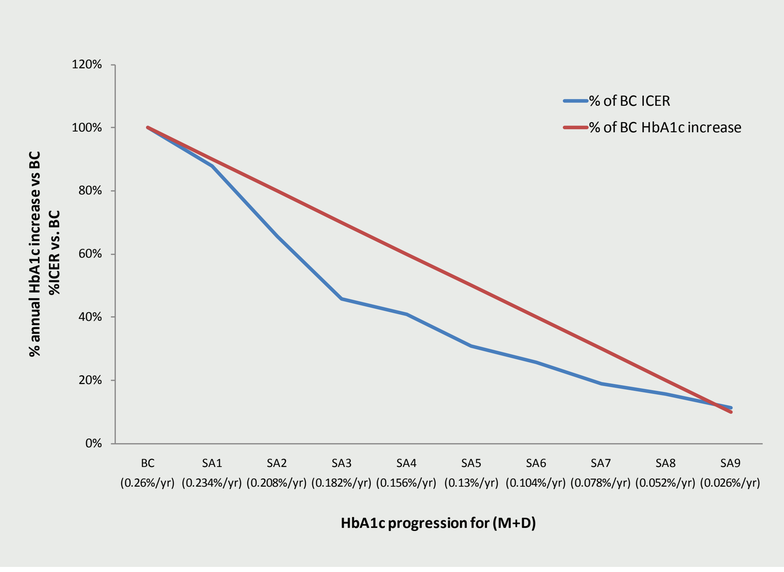


Figure 4) Average time to treatment escalation for M+S versus M+D



Conclusion

Glycaemic durability is known to be associated with both patient phenotype and choice of therapy.

This analysis demonstrates that the annual rate of increase in HbA1c exerts considerable influence over predicted cost effectiveness and is therefore an important variable to study when assessing the value for money of new interventions in the management of type 2 diabetes.

References

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