RESEARCH POSTER SESSION 3, DIABETES/ENDOCRINE/METABOLIC DISORDERS **PDB95**

RISK FACTOR CLUSTERING AND THE ECONOMIC MODELING OF TYPE 2 DIABETES MELLITUS (T2DM)

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BACKGROUND

- Efficient resource allocation requires evaluating the full cost and health consequences of competing treatment paths (i.e., cost-effectiveness analysis)
- For chronic and progressive diseases like T2DM, this requires evaluation over long time horizons
- Because clinical trials are seldom long enough to capture this long-time horizon, economic modeling techniques are routinely used to support economic evaluation in T2DM[1-4]
- Given the complexity of T2DM (e.g., complications involving multiple organ systems which often take years or even decades to develop and event rates that tend to accelerate over time, complications that not only share common risk factors but the presence of one can also serve to increase the risk for development of the others, and multifactorial treatment patterns that frequently require intensification over time),[5] patient-level micro-simulation models that use risk prediction equations to convert biomarker values into event risks is the norm
- Though risk factor clustering (whereby individuals with one unfavorable risk factor are likely to have other unfavorable risk factors as well) is common in T2DM populations, accounting for it in empirical applications is rare despite the longstanding example of the Global Diabetes Model (GDM)[6]
- The absence of capturing risk factoring clustering in economic modeling of T2DM can potentially bias estimates of cost-effectiveness
- While the GDM approach is data-intensive, the problem can also be addressed in micro-simulation by modeling correlation of risk factors at the time that baseline patient characteristics are randomly drawn for each hypothetical patient
- Not aware of publicly available risk factor correlation matrices for T2DM

OBJECTIVE

This study aimed to leverage National Health and Nutrition Examination Survey (NHANES) data to estimate correlation coefficients and fill the gap in the literature. This study also aims to investigate the potential impact of ignoring risk factor clustering for hypothetical interventions in 2nd and 3rd lines of therapy from a US 3rd party payer perspective.

METHODS

Calculation of Correlation Matrix

- We pooled and used 5 cross-sections (2007-2008, 2009-2010, 2011-2012, 2013-2014, and 2015-2016) from the NHANES,[7] which included 50,588 subjects in the U.S.
- We identified 3,209 individuals with T2DM, using self-reported diabetes for subjects aged 30 to 79 years and not on insulin or on insulin that was started 1 year after diagnosis[8]
- We defined two sub-groups of individuals with T2DM, which are frequently relevant for economic evaluation: subjects treated with a biguanide only (n = 347) and subjects treated with both a biguanide and a sulfonylurea (n = 169)
- We calculated correlation coefficients for age, HbA1c, total cholesterol, LDL, HDL, triglycerides, SBP, and BMI for each cohort using sample weights for the 5 cross-sections provided by NHANES (combined full sample 2 year interview weight, assuming the average of the variances from the strata with multiple sampling units for each stratum with one sampling unit).
- Only subjects with values for all risk factors were included in the analysis to ensure a positive semi-definite correlation matrix

Economic Evaluation of Hypothetical Intervention

- We estimated the impact of capturing risk factor clustering on cost-effectiveness results by performing a hypothetical economic evaluation with and without including correlation between the risk factors, separately for a cohort treated with biguanide only and for a cohort treated with a biguanide + a sulfonylurea
- The US 3rd party payer perspective was adopted with a discount rate of 3% for both costs and health benefits (Table 1). A comprehensive validated economic microsimulation model, the Economics and Health Outcomes model of T2DM (ECHO-T2DM), was used.[9,10] The structure and flow of ECHO-T2DM are depicted in Box 1. Macrovascular risks were simulated using UKPDS-OM2.[11]
- To ensure stable results, 1,000 cohorts of 2,000 unique hypothetical patients (i.e., 2 million patients) were simulated.
- For the hypothetical intervention arm, a HbA1c lowering of 1.0% and SBP lowering of 5 mmHg was assumed. For the hypothetical comparator, a HbA1c lowering of 0.5% was assumed. Table 2 presents all treatment effects
- Biomarker changes (e.g., HbA1c, SBP, BMI) were updated annually to account for the impact of therapies and the natural "drifts" in these markers overtime (Table 1)
- When additional glycemic lowering was needed to maintain HbA1c <7.0%, basal insulin was initiated at 10 IU and titrated over time to a maximum of 60 IU; if further insulin was needed to maintain glycemic control, prandial insulin was added starting at 5 IU and titrated to a maximum of 200 IU. Both basal and prandial insulin regimens were associated with an increased risk of hypoglycemia (1.98 and 10.28 events per PY and 0.005 and 0.042 event per PY for non-severe and severe hypoglycemia respectively)
- Unit Costs and QALY disutility weights sourced from the literature[12-15] (Table 3)

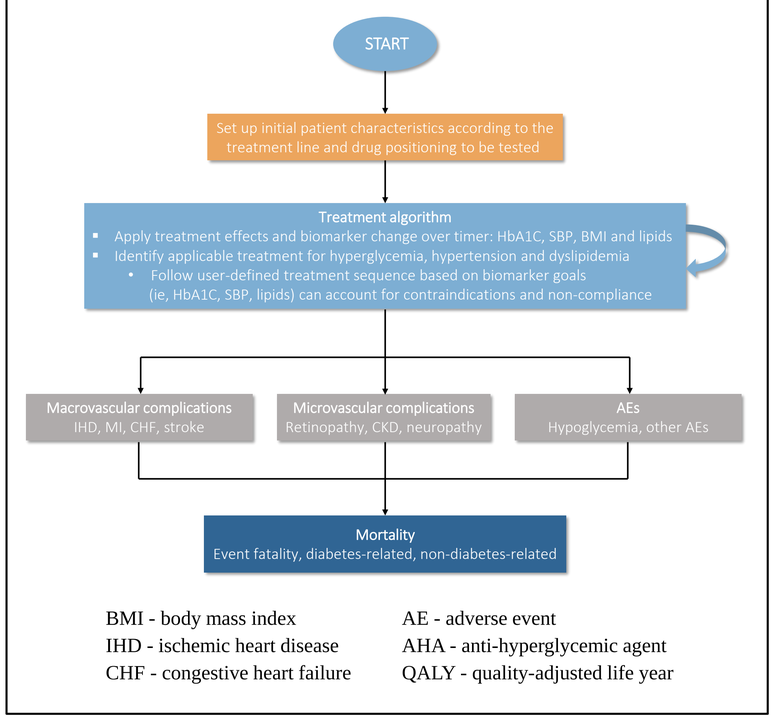
Table 1: Key Modeling Assumptions

Parameter	Assumption
Time horizon	20 years
Discount rate	3.0%
Annual drifts	
HbA1c[16]	0.14%
SBP[16]	0.3 mmHg
Lipids[17]	0.3 mg/dL
BMI	0 kg/m^2
HbA1c Target	<7.0%

Table 2: Hypothetical Treatment Profiles

Treatment effects	Intervention	Comparator
HbA1c, %	-1.0	-0.5
SBP, mmHg	-5.0	0.0
BMI, kg/m^2	-0.5	-0.5
Rates of AEs		
Non-severe symptomatic hypoglycemia	0.005	0.005

Box 1: Overview of ECHO-T2DM



BMI - body mass index
IHD - ischemic heart disease
CHF - congestive heart failure
AE - adverse event
AHA - anti-hyperglycemic agent
QALY - quality-adjusted life year

Table 3: Unit Costs and QALY Disutility Weights

Health Outcome	Event ($)	Annual Follow-up ($)	QALY*
Baseline	--	--	1.027[14]
Patient Characteristics			
Age (per 10 Years)	--	--	-0.0235[14]
Female	--		-0.0930[14]
Duration of DM (per 10 Years)	--	--	-0.0163[14]
Macrovascular Complications			
IHD	26,761[12]	2,380[12]	-0.028[14]
MI	70,566[12]	2,380[12]	-0.028[14]
CHF	29,701[12]	2,380[12]	-0.028[14]
Stroke	52,656[12]	19,428[12]	-0.115[14]
Microvascular Complications			
BDR	88[12]	88[12]	0.000
ME	998[12]	88[12]	0.000
PDR	768[12]	88[12]	0.000
Blindness	3,578[12]	3,578[12]	-0.057[14]
Stage 1 CKD	0	0	0.000
Stage 2 CKD	0	6,695[13]	0.000
Stage 3a CKD	0	8,918[13]	-0.050[14]
Stage 3b CKD	0	8,918[13]	-0.050[14]
Stage 4 CKD	0	22,847[13]	-0.050[14]
Stage 5 CKD (but no ESRD)	0	22,847[13]	-0.070[14]
ESRD	0	89,655[12]	-0.200[14]
Symptomatic Neuropathy	1,098[12]	1,376[12]	-0.084[14]
PVD	158[12]	158[12]	-0.061[14]
Diabetic Foot Ulcer	2,684[12]	1,032[12]	-0.170[14]
LEA	11,303[12]	2,158[12]	-0.272
Hypoglycemic Events			
Non-Severe Hypoglycemia	0	0	-0.0035[15]
Severe Hypoglycemia	665[12]	0	-0.0118[15]
Obesity			
Per 1 BMI > 25	--	--	-0.0061[14]

*QALY decrements for macrovascular and microvascular events and amputation are annualized. QALY decrements for hypoglycemic events are per event; BDR, background diabetic retinopathy; ME, macular edema; CKD, Chronic kidney disease; ESRD, end-stage renal disease; PVD, peripheral vascular disease; LEA, lower extremity amputation

RESULTS

- Sample descriptive statistics for the risk factors for individuals with T2DM treated with biguanides only and treated with a biguanide + a sulfonylurea are presented in Table 4. Subjects in the biguanide only cohort were modestly younger, had shorter diabetes duration, had lower HbA1c, but were not generally healthier than those in the biguanide + sulfonylurea cohort.
- The estimated risk factor correlation coefficients for the biguanide only cohort are presented in Table 5 and those for the biguanide + sulfonylurea cohort are presented in Table 6.
  - The cholesterol components were in general tightly correlated for both cohorts
  - For the biguanide + sulfonylurea cohort, age was inversely correlated with HbA1c and cholesterol
  - Correlation was generally low for the other pairs of risk factors analyzed
- Economic evaluation results are presented in Table 7. There are important differences in the cost-effectiveness of the hypothetical intervention in treating patients in the two cohorts, with lower estimated ICERs for the biguanide + sulfonylurea cohort.
- The addition of the risk factor correlation coefficient had only a modest impact on the results, however, with an increase from $37,470 to $40,713 for the biguanide only cohort and a decrease from $26,307 to $23,639 for the biguanide + sulfonylurea arm.

Table 4: Patient Characteristics in NHANES, by Cohort

Parameter	Biguanide Only (N = 347) Mean (SD)	Biguanide + Sulfonylurea (N = 169) Mean (SD)
Demographics		
Age (years)	60.8 (11.6)	61.6 (9.4)
Males (%)	46.7%	56.8%
Caucasian (%)	100.0%	100.0%
Disease duration (years) (mean, SD)	6.9 (6.9)	9.9 (7.9)
Smokers	13.8%	17.4%
Clinical Indicators		
HbA1c (%)	6.9 (1.4)	7.7 (1.7)
SBP (mmHg)	129.4 (17.4)	130.0 (16.9)
BMI (kg/m2)	31.8 (7.0)	32.9 (7.6)
WBC (*10^6)#	6.9 (1.9)	6.9 (1.9)
HR (beat/minute)	73.8 (13.9)	73.2 (11.9)
Total Cholesterol (mg/dl)	178.7 (40.0)	173.4 (36.7)
LDL Cholesterol (mg/dl)	99.6 (33.6)	94.6 (32.3)
HDL Cholesterol (mg/dl)	49.2 (13.1)	45.7 (12.2)
Triglycerides (mg/dl)	148.9 (71.2)	165.4 (75.1)
eGFR (ml/min/1.73m2)	86.7 (20.7)	84.7 (17.7)
History of Co-Morbidities at Baseline (%)		
IHD (not including MI)	7.1%	8.2%
MI	9.1%	10.0%
CHF	7.9%	6.5%
Stroke	6.5%	6.4%
Microalbuminuria	15.20%	16.89%
Macroalbuminuria	2.99%	5.16%
ESRD	0.9%	0.6%

#Sourced from UKPDS 59[17]

Table 5: Correlation Coefficients for Baseline Risk Factor Values for Biguanide Only Cohort

	Age	HbA1c	Total Cholesterol	LDL	HDL	Triglycerides	SBP	BMI
Age	1.000							
HbA1c	-0.069	1.000						
Total Cholesterol	-0.205	-0.002	1.000					
LDL	-0.145	0.069	0.914	1.000				
HDL	0.014	-0.326	0.148	0.032	1.000			
Triglycerides	-0.206	0.110	0.484	0.226	-0.453	1.000		
SBP	0.149	0.242	0.019	-0.123	0.050	0.223	1.000	
BMI	-0.455	0.119	0.288	0.204	-0.175	0.403	-0.009	1.000

Table 6: Correlation Coefficients for Baseline Risk Factor Values Biguanide + Sulfonylurea Cohort

	Age	HbA1c	Total Cholesterol	LDL	HDL	Triglycerides	SBP	BMI
Age	1.000							
HbA1c	-0.445	1.000						
Total Cholesterol	-0.495	0.539	1.000					
LDL	-0.531	0.417	0.852	1.000				
HDL	-0.383	-0.146	-0.074	0.065	1.000			
Triglycerides	0.148	0.337	0.436	0.003	-0.746	1.000		
SBP	-0.119	-0.045	0.004	0.238	0.201	-0.365	1.000	
BMI	-0.143	0.067	0.000	-0.211	0.104	0.167	-0.247	1.000

Table 7: Cost-Effectiveness of the Hypothetical Intervention

	Biguanide Only Cohort						Biguanide + Sulfonylurea					
	Without Risk Factor Clustering			Risk Factor Clustering			Without Risk Factor Clustering			Risk Factor Clustering		
	Intervention	Comparator	Difference	Intervention	Comparator	Difference	Intervention	Comparator	Difference	Intervention	Comparator	Difference
Costs (Discounted $2018)												
Treatment												
Non-Insulin AHA	9,276	3,071	6,205	9,375	3,092	6,283	6,811	2,177	4,634	6,535	2,056	4,478
Insulin AHA	19,273	22,409	-3,137	19,964	23,201	-3,236	42,536	45,443	-2,907	45,803	48,791	-2,988
Macro- and Microvascular Complications												
Macrovascular	50 539	51,570	-1,031	50,299	51,242	-942	49,836	50,485	-649	49,945	50,643	-698
Microvascular	36,972	36,824	148	37,766	37,579	187	36,817	36,753	64	37,146	36,951	195
Hypoglycemia	38	46	-7	37	43	-6	92	101	-8	93	100	-6
Total Costs	116,097	113,920	2,178	117,441	115,156	2,285	136,092	134,959	1,133	139,522	138,541	981
Health Outcomes (Discounted)												
LY's	10.769	10.707	0.062	10.933	10.873	0.059	10.588	10.544	0.044	10.666	10.623	0.044
QALY's	7.433	7.375	0.058	7.553	7.497	0.056	7.285	7.242	0.043	7.303	7.262	0.042
Survival at End of Year 20	35.0%	34.6%	0.4%	36.2%	35.7%	0.4%	31.9%	31.6%	0.3%	32.2%	31.9%	0.3%
Incremental Cost Per QALY Gained			**37,470**			**40,713**			**26,307**			**23,639**

DISCUSSION

- Risk factor clustering in patients with T2DM (with genetic and behavioral sources) is widely understood but seldom modeled. To fill a gap in the literature and hopefully spur greater adoption in economic modeling, we estimated bivariate correlations for a number of key T2DM risk factors. The correlations were naturally largest (in absolute value) for the cholesterol components, but age was also unexpectedly inversely related with HbA1c and the cholesterol components in the biguanide + sulfonylurea cohort (perhaps indicative of a survival effect). Many of the other correlation coefficients were relatively close to 0.
- We tested the impact of risk factor clustering empirically for two common patient cohorts and a hypothetical intervention, finding a modest impact on cost-effectiveness (in both directions). While the differences did not affect assessment of cost-effectiveness qualitatively in this example, the results diverged enough to suggest that it could play an important role in real applications. In particular, it is conceivable that the impact is larger in special patient sub-groups (e.g., CV or morbidly obese patients).
- While weighted to reflect the US population of individuals with T2DM, it must be acknowledged that the sample sizes are relatively small. Moreover, the set of risk factors was limited by those for which risk factor clustering is supported in the model used. In the future, more risk factors should be considered.
- For economic analysis, it is common to condition patients at baseline to failing on therapy (thus the need for a treatment change). This was not possible with the current data set, given limited sample sizes.
- Future research should be undertaken to estimate benchmark correlation coefficients for additional patient groups of interest, including untreated patients, patients with macro-vascular disease, patients with renal disease, patients with morbid obesity, and for patients in other regions of the world.

CONCLUSION

Capturing risk factor clustering may improve estimates of long-term cost-effectiveness of T2DM interventions using economic modeling. Using correlation between risk factors in sampling baseline characteristics is easy and now two sets of correlation coefficients (albeit crude) are available.

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