



University
of Dundee



A COMPARATIVE STUDY ON RESPONSE TO DPP-4I, SU AND TZD

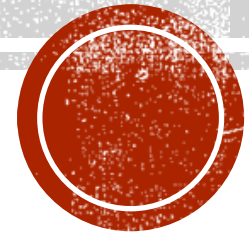
IN DIABETIC PATIENTS FROM **DIFFERENT ETHNIC GROUPS**

Ewan R Pearson

Viswanathan
Mohan



Sushrma Gan



OUTLINE

- Meta-analysis
- DPP-4I
 - Scottish
 - Indian
 - Comparison
 - Candidate Gene Study
 - GRS
- SU
 - Scottish
 - Indian
 - Comparison
- TZD
 - Scottish
 - Indian
 - Comparison
- Present Status





Efficacy of Modern Diabetes Treatments DPP-4i, SGLT-2i, and GLP-1RA in White and Asian Patients With Diabetes: A Systematic Review and Meta-analysis of Randomized Controlled Trials

*Sushrima Gan,¹ Adem Y. Dawed,¹
Louise A. Donnelly,¹ Anand T.N. Nair,¹
Colin N.A. Palmer,¹ Viswanathan Mohan,²
and Ewan R. Pearson¹*

Diabetes Care 2020;43:1948–1957 | <https://doi.org/10.2337/dc19-2419>



RESPONSE TO COMMENT ON GAN ET AL.

Efficacy of Modern Diabetes Treatments
DPP-4i, SGLT-2i, and GLP-1RA in White
and Asian Patients With Diabetes: A
Systematic Review and Meta-analysis of
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Diabetes Care 2020;43:e1–e2 | <https://doi.org/10.2337/dci20-0049>

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RESULTS META-ANALYSIS

<u>DPP-4 inhibitors</u>		
Ethnicity	Number of studies	Mean difference (95% CI)
Asian	9	-0.62[-0.80,-0.45]
White	17	-0.47[-0.57,-0.37]
Test for sub-group differences (p value)		0.1366
<u>SGLT-2 inhibitors</u>		
Ethnicity	Number of studies	Mean difference (95% CI)
Asian	7	-0.96[-1.10,-0.82]
White	9	-0.64[-0.74,-0.53]
Test for sub-group differences (p value)		0.0003
<u>GLP-1RA</u>		
Ethnicity	Number of studies	Mean difference (95% CI)
Asian	3	-0.77[-0.86,-0.67]
White	20	-0.76[-1.19,-0.33]
Test for sub-group differences (p value)		0.9612

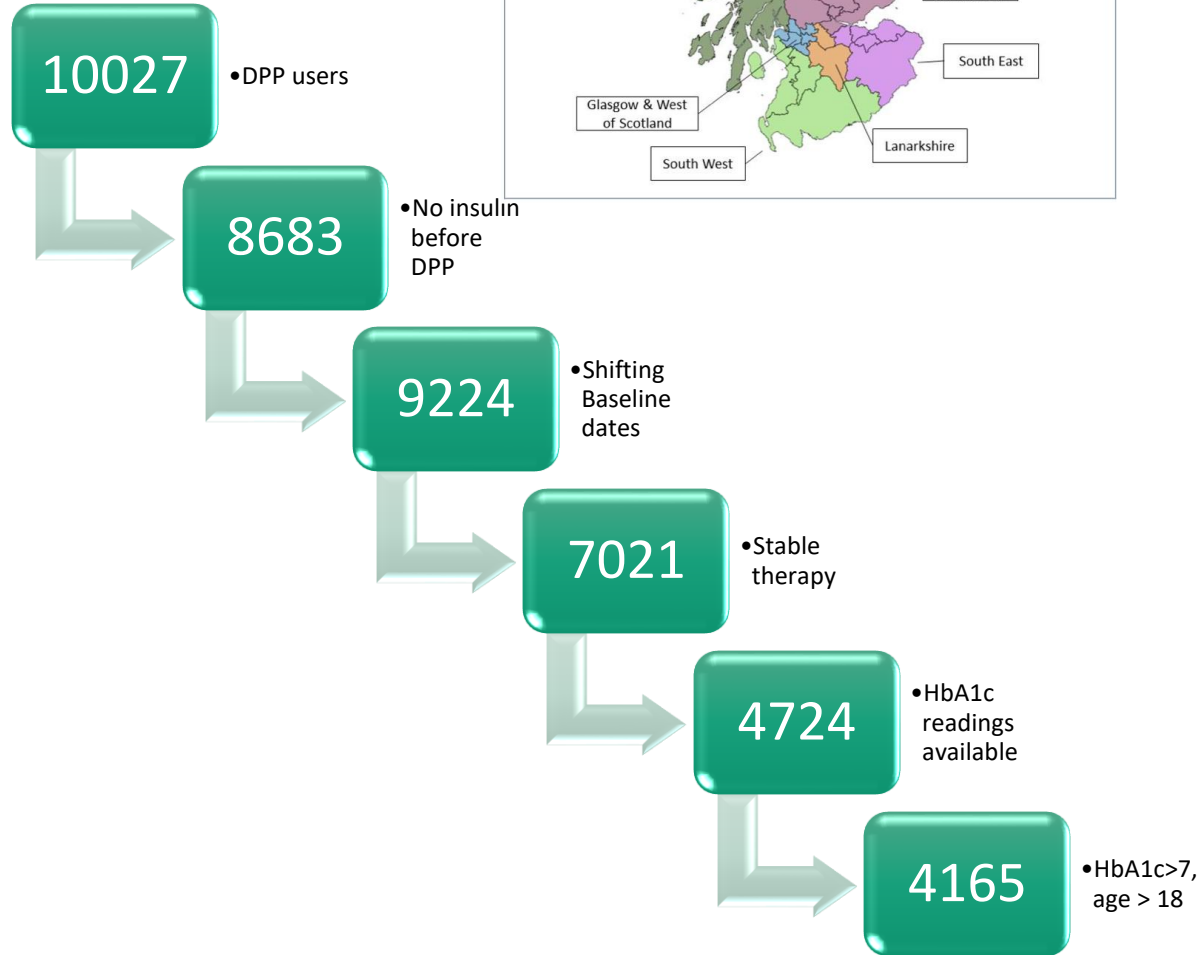
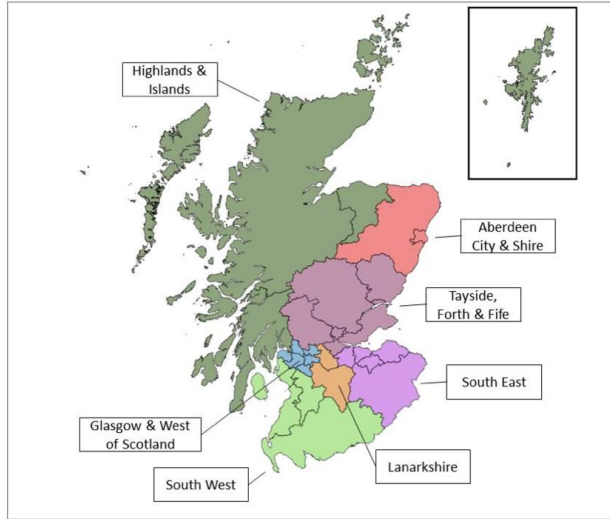
SUB-GROUP ANALYSIS



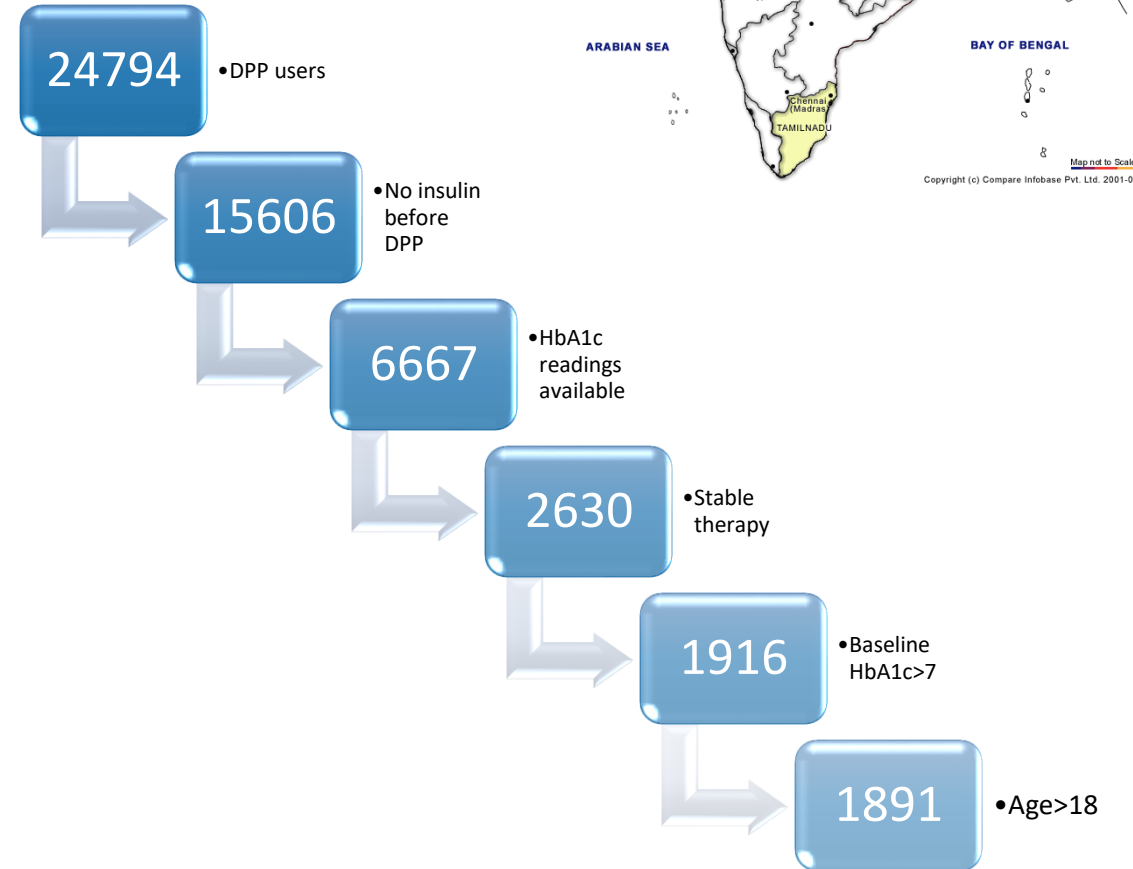
DPP-4I



T & F.



MDRF



Tayside & Fife - Univariate

Variables	Number with valid baseline data	Beta coefficient	SE	p-value
Age at diagnosis	4165	0.007	0.001	0.0002
Duration of Diabetes	4165	-0.004	0.003	0.339
BMI	3392	-0.011	0.003	0.002
Baseline Gap	4165	-1.73E-05	1.13E-03	0.988
Sex M	4165	0.07	0.04	0.0857.
Therapy MonoDual	2320	-	-	-
Therapy Triple or more	1845	-0.07	0.04	0.08.
Treatment Gap	4165	-0.004	0.0006	2.5e-13***
log(HDL-c)	3755	-0.108	0.089	0.224
log(LDL-c)	1440	-0.005	0.081	0.954
log(Triglycerides)	1565	0.096	0.065	0.143
log(Cholesterol)	3755	-0.03	0.09	0.738
log(non-HDL cholesterol)	3755	0.004	0.07	0.949
Creatinine	3735	0.0012	0.0008	0.121
log(C-peptide)	860	0.096	0.09	0.313
Baseline HbA1c	4165	0.411	0.01	<2e-16***

Tayside & Fife - Multivariate

	Beta coefficient	SE	p-value
Age at diagnosis	0.005	0.002	0.0127
BMI	-0.008	0.003	0.0113
Sex M	0.11	0.045	0.0149
log non-HDL Cholesterol	-0.32	0.072	1.41E-05
Therapy Mono Dual	-	-	-
Therapy 3 or more	-0.18	0.045	9.19E-03
Treatment gap	-0.004	0.0007	4.23E-09

MDRF – Univariate Analysis

	Number with valid baseline data	Beta coefficient	SE	p-value
Age at diagnosis	1891	0.0009	0.003	0.766
Duration of Diabetes	1891	-0.034	0.005	7.19e-09**
BMI	1832	-0.0007	0.006	0.917
Baseline Gap	1891	0.011	0.001	<2e-16***
Sex	1891	0.09	0.06	0.105
Therapy MonoDual	1593	-	-	-
Therapy Triple or more	298	-0.13	0.08	0.106
Treatment Gap	1891	0.001	0.0005	0.0368*
log(HDL-c)	1413	-0.2578	0.165	0.118
log(LDL-c)	1371	0.311	0.099	0.0017**
log(Triglycerides)	1426	0.25	0.07	0.00054***
log(Cholesterol)	1417	0.529	0.149	0.000418***
log(Creatinine)	1412	0.102	0.14	0.469
log(HOMA-B)	379	-0.69	0.14	1.66e-06***
log(HOMA-IR)	379	0.7522	0.208	0.000349***
log(C-peptide Fasting)	381	0.192	0.243	0.43
log(C-peptide Stimulated)	381	-0.553	0.246	0.0256*

MDRF - Multivariate

	Beta coefficient	SE	p-value
Age at diagnosis	0.008	0.002	0.00016
Duration of Diabetes	-0.013	0.004	0.002

	Beta coefficient	SE	p-value
Age at diagnosis	0.01	0.005	0.04
Duration of Diabetes	-0.03	0.01	0.04
HOMA-B	0.004	0.001	0.01

India Scotland Data Combined- DPP 4i

Coefficients	Estimate	SE	Pr(> t)
Baseline HbA1c	0.514	0.013	<2e-16***
BMI	-0.007	0.002	0.005**
Age_at_diag	0.008	0.002	4.68e-07***
SexM	0.108	0.033	0.00133**
Group_Scot	-0.699	0.04	<2e-16***

Residual standard error: 1.166 on 5218 degrees of freedom
(832 observations deleted due to missingness)
Multiple R-squared: 0.2339, Adjusted R-squared: 0.2331
F-statistic: 318.6 on 5 and 5218 DF, p-value: < 2.2e-16

> |



VARIANTS INCLUDED (BETA CELL FUNCTION) DPP-4I RESPONSE

index_SNP	chr	Risk allele	OR	gene	MAF
rs2075423	1	G	1.07	PROX1	0.332
rs10203174	2	C	1.14	THADA	0.100
rs1496653	3	A	1.09	UBE2E2	0.201
rs11717195	3	T	1.11	ADCY5	0.238
rs4402960	3	T	1.13	IGF2BP2	0.328
rs7756992	6	G	1.17	CDKAL1	0.276
rs17168486	7	T	1.11	DGKB	0.160
rs3802177	8	G	1.14	SLC30A8	0.303
rs11257655	10	T	1.07	CDC123/CAMK1	0.192
rs7903146	10	T	1.39	TCF7L2	0.326
rs231361	11	A	1.09	KCNQ1	0.325
rs163184	11	G	1.09	KCNQ1	0.483
rs1552224	11	A	1.11	ARAP1(CENTD	0.178
rs10830963	11	G	1.1	MTNR1B	0.269
rs1359790	13	G	1.08	SPRY2	0.298
rs4502156	15	T	1.06	C2CD4A	0.432



C2CD4A

rs4502156

index_SNP	chr	Risk allele	OR	gene	MAF	
rs4502156	15	T	1.06	C2CD4A	0.432	rs4502156_T

Genotypes:

	frequency	percentage
C/C	299	31.74098
C/T	477	50.63694
T/T	166	17.62208
NA's	189	

Alleles:

	frequency	percentage
C	1075	57.05945
T	809	42.94055
NA's	378	

HWE (p value): 0.3192721

SNP: rs4502156_geno adjusted by:

	dif	lower	upper	p-value	AIC
log-Additive					
0,1,2	-0.1281	-0.2526	-0.003637	0.04396	3231

MODEL

```
Call:
lm(formula = hbaic_outcome ~ hbaic_base_value + grs, data = merge15)

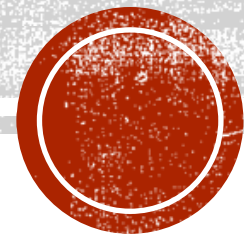
Residuals:
    Min       1Q   Median       3Q      Max
-5.1744 -0.5524  0.1522  0.7977  3.8948

Coefficients:
              Estimate Std. Error t value Pr(>|t|)
(Intercept)   -2.64268    0.34449   -7.671 4.96e-14 ***
hbaic_base_value  0.37575    0.03593   10.458 < 2e-16 ***
grs            -0.03228    0.11906   -0.271  0.786
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Residual standard error: 1.244 on 799 degrees of freedom
(329 observations deleted due to missingness)
Multiple R-squared:  0.1204,    Adjusted R-squared:  0.1182
F-statistic: 54.68 on 2 and 799 DF,  p-value: < 2.2e-16
```



SU



DATA CLEANING - SU

Tayside & Fife

SU Users

27323

Shifting
Baseline Date
25510

No insulin
before SU
24972

Stable
treatment
24938

HbA1c
available
14132

Age>18,
Duration>0
• 11047

MDRF

SU Users

52983

No insulin before
SU
40287

HbA1c available
13664

Stable treatment
5006

Age>18,
Duration>0
5006



BASELINE ADJUSTED MODEL SCOTTISH -SU

Variable	Number	Estimate	SE	P-value
Age at diagnosis	11044	0.0176	0.0010	<2e-16***
Duration of Diabetes	11044	-0.0332	0.0027	<2e-16***
Sex M	11044	0.2406	0.0263	<2e-16***
BMI baseline	11023	-0.0236	0.0023	<2e-16***
Log C-peptide	2711	0.2204	0.0397	7.14e-09***
Log HDL	8364	0.167	0.05	0.0033**
Log LDL	3077	-0.0002	0.053	0.997
Log Trigs	3607	-0.11086	0.0407	0.00648**
Log Cholesterol	8754	-0.137	0.057	0.0164*
Log Creatinine	9696	0.358	0.043	<2e-16***
Baseline Gap ^(Baseline date- HbA1c base date)		-0.0057	0.0006	<2e-16***
Therapy		Mono(3783)		
Dual	6109	-0.1916	0.028	1.24e-11***
Triple or more	1155	-0.4722	0.0459	<2e-16***



MULTIVARIATE MODEL

Variable	Estimate	SE	P-value
Age at diagnosis	0.0091	0.0043	0.0854.
Duration of Diabetes	-0.023	0.0089	0.00932***
Sex M	0.3358	0.084	8.32e-05***
BMI baseline	-0.027	0.007	0.00049***
Log C-peptide	0.285	0.0711	6.6e-05***
Log Trigs	-0.218	0.073	0.00301**

Variable	Estimate	SE	P-value
Age at diagnosis	0.014	0.002	6.96e-10***
Duration of Diabetes	-0.023	0.0089	0.00932***
Sex M	0.245	0.052	3.09e-06***
BMI baseline	-0.019	0.004	1.70e-06***
Log Trigs	-0.088	0.044	0.0479*

Removing
trigs :
8255



BASELINE ADJUSTED MODEL INDIAN -SU

Variable	Number	Estimate	SE	P-value
Age at diagnosis	5006	0.00303	0.004	0.452
Duration of Diabetes	5006	-8.579e-05	3.298e-05	0.00931 **
Sex M	5006	0.1684	0.0866	0.0519 .
BMI baseline	4846	-0.01248	0.0106	0.242
Log C-peptide(Fast)	1266	-0.24898	0.07905	0.00167 **
Log HDL	3646	-2.856e-05	1.669e-03	0.986
Log LDL	3525	-0.0004023	0.0004436	0.365
Log Trigs	3692	-0.07371	0.03062	0.0161 *
Cholesterol	3707	-0.0008378	0.0003727	0.0246 *
Log Creatinine	3651	-0.23085	0.30244	0.445
Homa B	1259	0.0018763	0.0005542	0.000732 ***
Homa IR	1259	-0.08445	0.02340	0.000319 ***



MULTIVARIATE MODEL

Variable	Estimate	SE	P-value
Duration of Diabetes	-1.268e-04	2.807e-05	6.90e-06 ***
Log C pep Fast	-0.4615151	0.0878766	1.77e-07 ***
HOMA B	0.0033292	0.0006142	7.13e-08 ***



India Scotland Data Combined- SU

Coefficients	Estimate	SE	Pr(> t)
Baseline HbA1c	0.781	0.013	<2e-16***
BMI	-0.012	0.004	0.00236**
Age_at_diag	0.014	0.002	3.74e-12***
SexM	0.275	0.046	3.94e-09***
Group_Scot	-0.378	0.06	8.22e-10***

Residual standard error: 2.346 on 10668 degrees of freedom
(2586 observations deleted due to missingness)
Multiple R-squared: 0.243, Adjusted R-squared: 0.2427
F-statistic: 685 on 5 and 10668 DF, p-value: < 2.2e-16

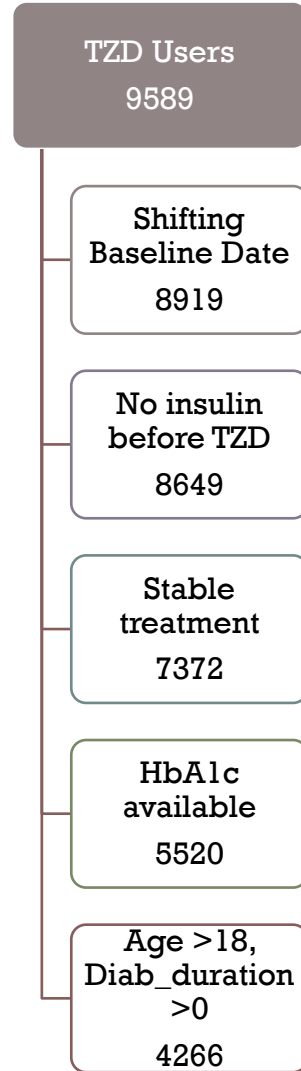


TZD

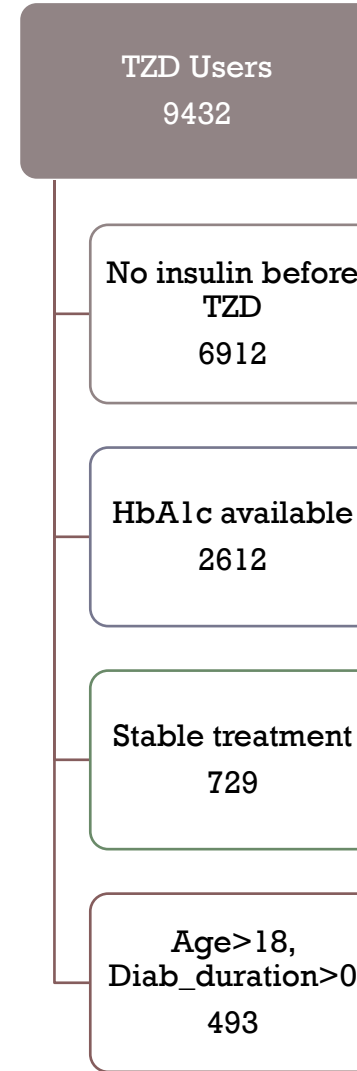


DATA CLEANING - TZD

Tayside & Fife



MDRF



Baseline Adjusted
Model Scottish- TZD

Variable	Number	Estimate	SE	P-value
Age at diagnosis	4266	0.0177	0.0018	<2e-16***
Duration of Diabetes	4266	-0.016	0.0038	2.87e-05***
Sex M	4266	-0.136	0.04	0.000747***
BMI baseline	3231	0.0175	0.003	<2.34e-06***
Log (C-peptide)	1199	0.46	0.066	4.16e-12***
Log (HDL)	3495	-0.18	0.08	0.0342*
Log (LDL)	1220	-0.05	0.08	0.568
Log (Trigs)	1378	-0.005	0.059	0.658
Log (Cholesterol)	3495	-0.342	0.096	0.000363***
Log (Creatinine)	3736	0.418	0.073	1.18e-08***
Baseline Gap(Baseline date- HbA1c base date)	4265	-0.003	0.0009	0.000447***
Treatment Gap	4265	6.47e-05	4.41e-05	0.143
Therapy				
Dual	2407	-	-	-
Mono	238	-0.215	0.088	0.0147*
Triple or more	1621	-0.226	0.0767	6.15e-08***



Multivariate Model Scottish- TZD

Variable	Estimate	SE	P-value
Age at diagnosis	0.02	0.004	<2e-16***
Duration of Diabetes	-0.01	0.005	0.0468*
Sex M	-0.214	0.054	9.14e-05***
BMI baseline	0.02	0.004	<2.76e-08***
Log (Cholesterol)	-0.465	0.109	2.32e-05***
Log (Creatinine)	0.34	0.096	0.000396***
Baseline Gap(Baseline date- HbA1c base date)	-0.003	0.001	0.003399***



Baseline Adjusted
Model Indian- TZD

Variable	Number	Estimate	SE	P-value
Age at diagnosis	493	0.004	0.004	0.09
Duration of Diabetes	493	-0.02	0.009	0.00528***
Sex M	493	-0.076	0.08	0.395
BMI baseline	475	-0.009	0.011	0.425
Log (C-peptideF)	30	-0.03	0.37	0.933
Log (C-peptideS)	30	0.41	0.47	0.386
Log (HDL)	363	0.189	0.22	0.404
Log (LDL)	352	-0.115	0.17	0.504
Log (Trigs)	364	0.04	0.102	0.693
Log (Cholesterol)	367	-0.02	0.255	0.923
Log (Creatinine)	381	-0.288	0.236	0.223
Treatment Gap	490	-0.003	0.001	0.0547 .
Therapy				
Dual	266	-	-	-
Mono	67	0.38	0.12	0.003**
Triple or more	160	-0.16	0.09	0.089.

Multivariate Model Indian- TZD

Variable	Estimate	SE	P-value
Baseline HbA1c	0.825	0.009	<2e-16***
Duration of Diabetes	-0.02	0.009	0.00528*



India Scotland Data Combined- TZD

Coefficients	Estimate	SE	Pr(> t)
Baseline HbA1c	0.506	0.014	<2e-16***
BMI	0.022	0.003	1.39e-10**
Age_at_diag	0.021	0.002	<2e-16***
SexM	-0.076	0.042	0.0719.
Group_Scot	-0.871	0.069	<2e-16***

Residual standard error: 1.243 on 3717 degrees of freedom
 (1055 observations deleted due to missingness)
 Multiple R-squared: 0.2545, Adjusted R-squared: 0.2534
 F-statistic: 253.7 on 5 and 3717 DF, p-value: < 2.2e-16



India Scotland Data Combined- TZD

Coefficients	Estimate	SE	Pr(> t)
Baseline HbA1c	0.506	0.014	<2e-16***
BMI	0.023	0.003	2.53e-16**
Age_at_diag	0.021	0.002	<2e-16***
Group_Scot	-0.876	0.069	<2e-16***

Residual standard error: 1.244 on 3718 degrees of freedom
(1055 observations deleted due to missingness)
Multiple R-squared: 0.2538, Adjusted R-squared: 0.253
F-statistic: 316.1 on 4 and 3718 DF, p-value: < 2.2e-16





DPP4i

✓ ANALYSIS



✓ ANALYSIS



DPP4i

✓ ANALYSIS

SU

✓ ANALYSIS

TZD

✓ ANALYSIS

SU

✓ ANALYSIS

TZD

✓ ANALYSIS



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