Statistical Analysis in G-SRS

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Comparing Adverse Events in G-SRS

- Identify common substances between:

Lactic Acidosis	vs.	Other Adverse Events (Aplastic Anemia, Hemolytic Anemia, Colitis Ischaemic, etc.)

- Use PRR as a metric of association

What is PRR?

PRR = Proportional Reporting Ratio

is The degree of disproportionate reporting of an AE for a product of interest compared to this same event for all other products

	Event Y	All other events	
Product X	a	b	a + b
All other products	c	d	c + d
	a + c	b + d	Total

PRR = [a/(a+b)] / [c/(c+d)] → If PRR >> 1 then Event Y is "disproportionately reported for Product X

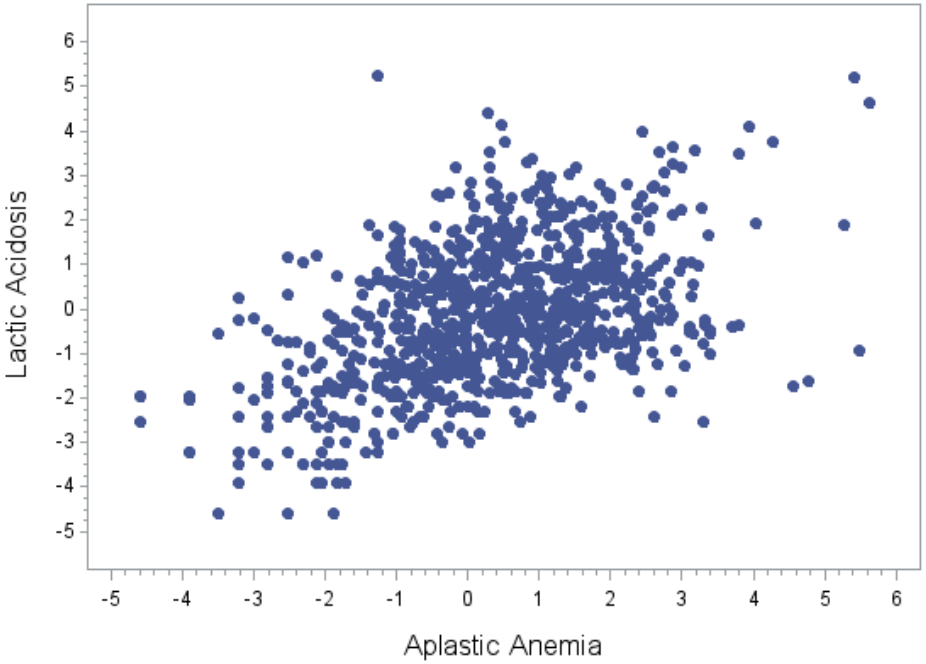
Issues with PRR:

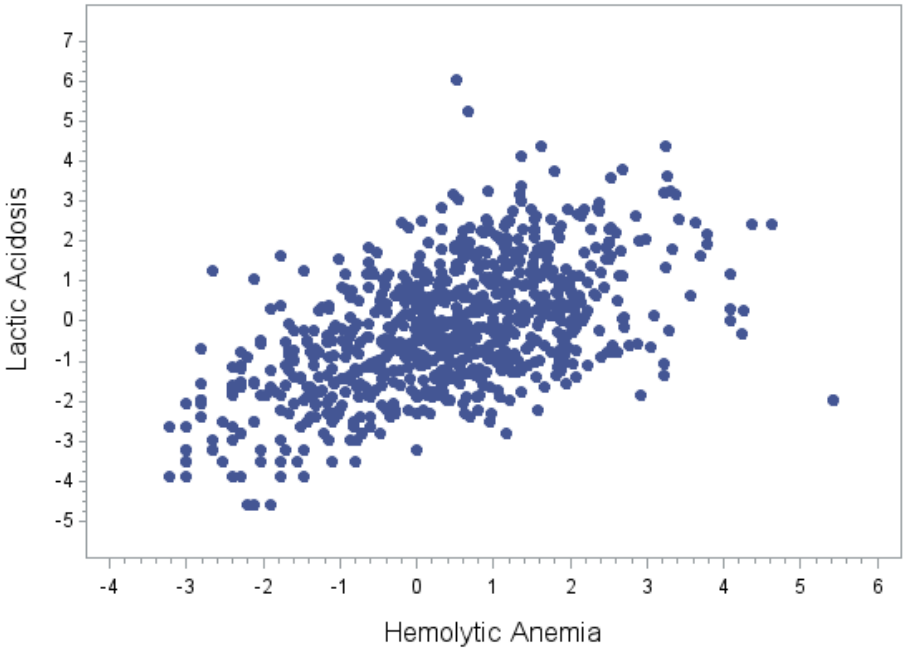
1. It does not adjust for small counts
2. Every report represents a suspicion of an AE related to a product

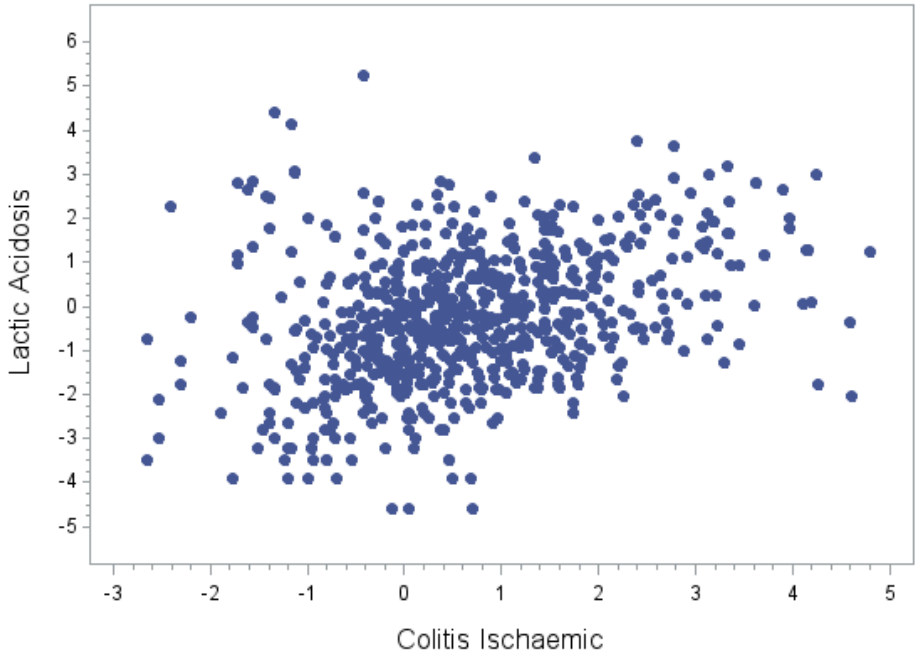
Comparing Adverse Events in G-SRS

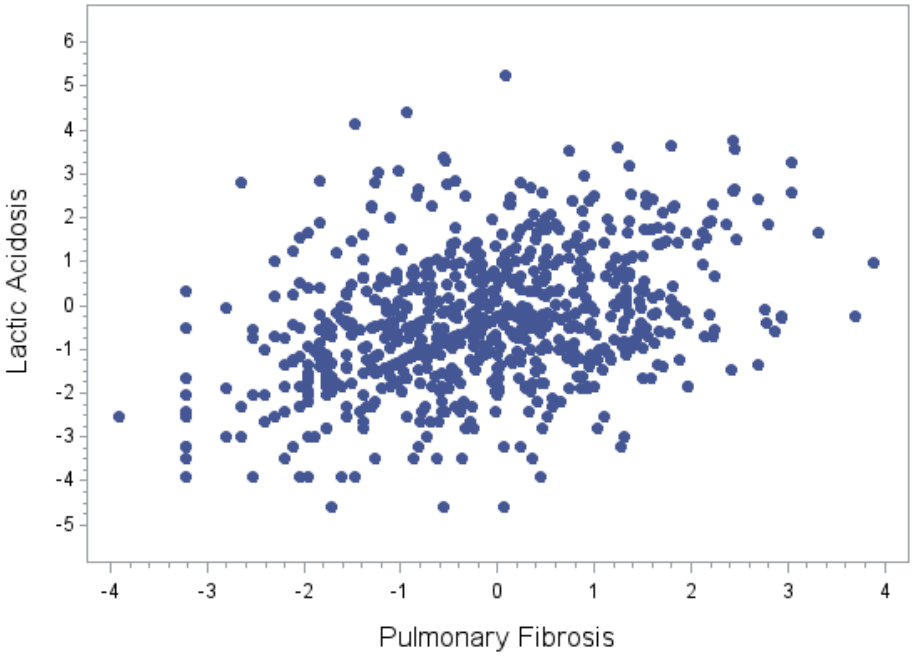
- Typically there are too many small values, so that the distribution of PRR would be highly skewed to the left.

- Transform the PRR values using Log_e:
  - Normalization
  - Valid statistical inference
  - Better graphics


Lactic Acidosis
Aplastic Anemia


Lactic Acidosis
Hemolytic Anemia


Lactic Acidosis
Colitis Ischaemic


Lactic Acidosis
Pulmonary Fibrosis

Pairwise analysis Lactic Acidosis (N=1203) vs. DME's

	DME Adverse Event	No. Substances	No. Common Substances with Acidosis	%Common	Correlation Coefficient
1	Liver necrosis	1534	933	61	0.6522
2	Acute pancreatitis	1915	1095	57	0.6262
3	Rhabdomyolysis	1660	984	59	0.6035
4	Liver failure	1840	1058	58	0.5967
5	Toxic epidemal necrolysis	1923	984	51	0.5667
6	Renal failure	2517	1170	46	0.5629
7	Hemolytic anemia	1312	874	67	0.5562
8	Stevens Johnson syndrome	2037	1016	50	0.5537
9	Haemolysis	1095	792	72	0.5204
10	Disseminated intravascular coagulation	1505	951	63	0.5156
11	Ventricular fibrillation	1343	884	66	0.5061
12	Tosade de Pointes	883	648	73	0.5059
13	Acute respiratory failure	2257	1131	50	0.4985
14	Pancytopenia	1752	993	57	0.4747
15	Product infectious disease transmission	399	268	67	0.4739
16	Sudden death	1379	903	65	0.4698
17	Aplastic anemia	1526	933	61	0.4522
18	Agranulocytosis	2109	1079	51	0.4466
19	Liver transplant	587	466	79	0.4107
20	Anaphylaxis and anaphylactoid reactions	2372	1066	45	0.4031
21	PML Progressive multifocal leukoencephalopathy	319	264	83	0.3986
22	TTP	681	545	80	0.3924
23	Pulmonary hypertension	1223	858	70	0.3824
24	Seizure	1301	869	67	0.3802
25	Congenital anomalies	947	606	64	0.3756
26	Pulmonary fibrosis	1078	769	71	0.3684
27	Colitis ischaemic	964	720	75	0.3542
28	Deaf	1546	938	61	0.3381
29	Suicide	1377	826	60	0.3303
30	Serotonin syndrome	758	556	73	0.3281
31	Blind	1618	953	59	0.2822
32	ALS Amyotrophic lateral sclerosis	376	334	89	0.2433
33	Neuroleptic malignant syndrome	691	475	69	0.1959
34	Endotoxic shock confirmed or suspected	1524	978	64	0.0033

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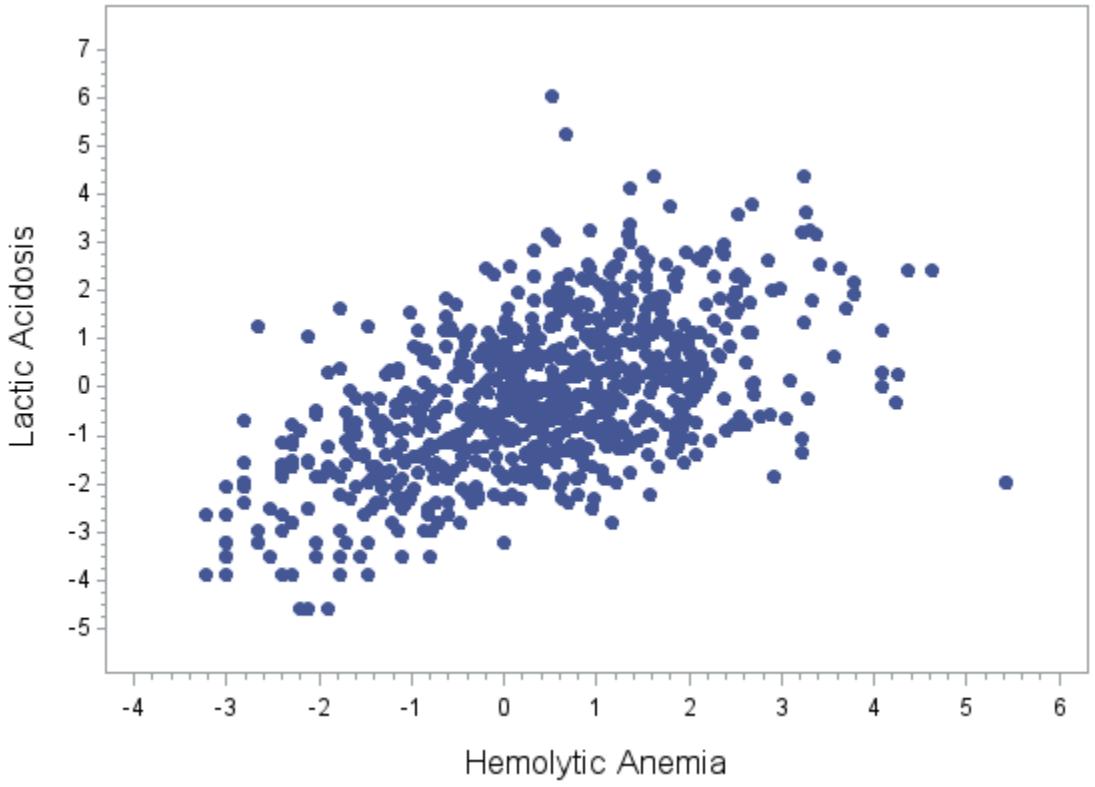
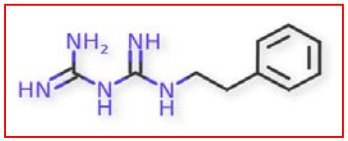
Lactic Acidosis vs. Hemolytic Anemia

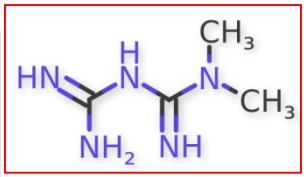


Lactic Acidosis vs. Hemolytic Anemia Outliers

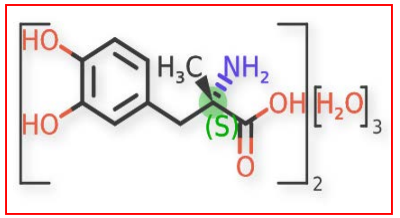


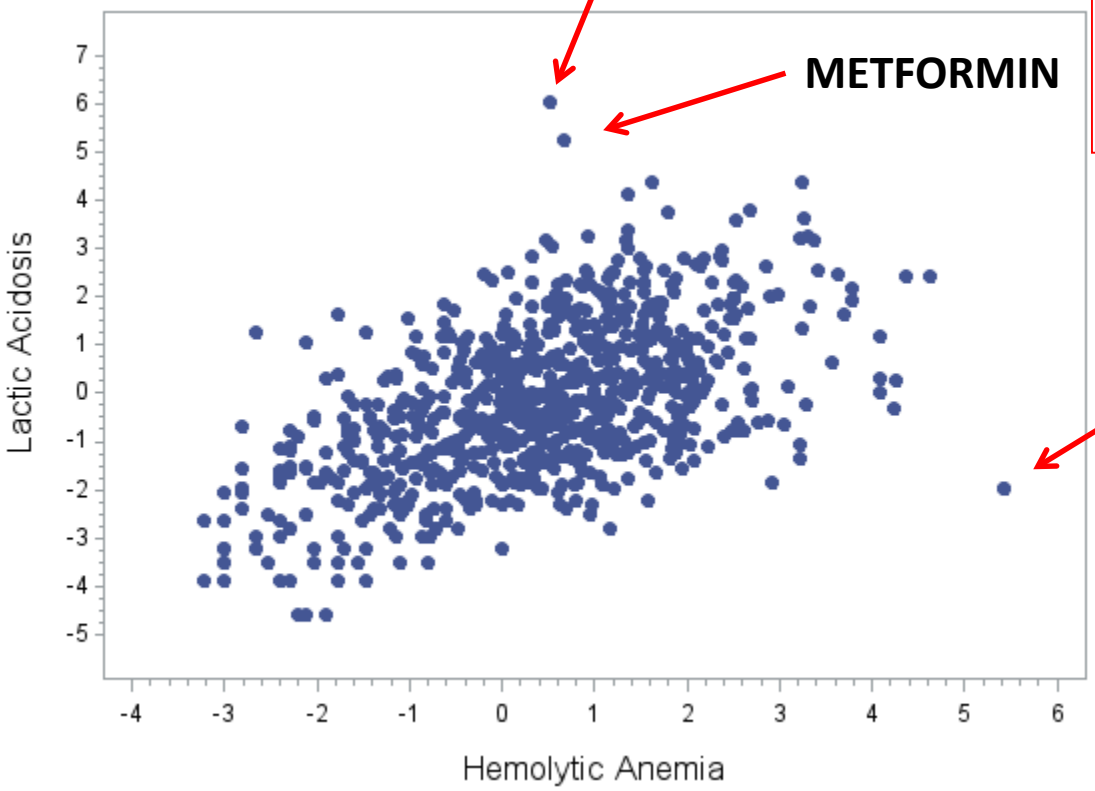
PHENFORMIN

METFORMIN

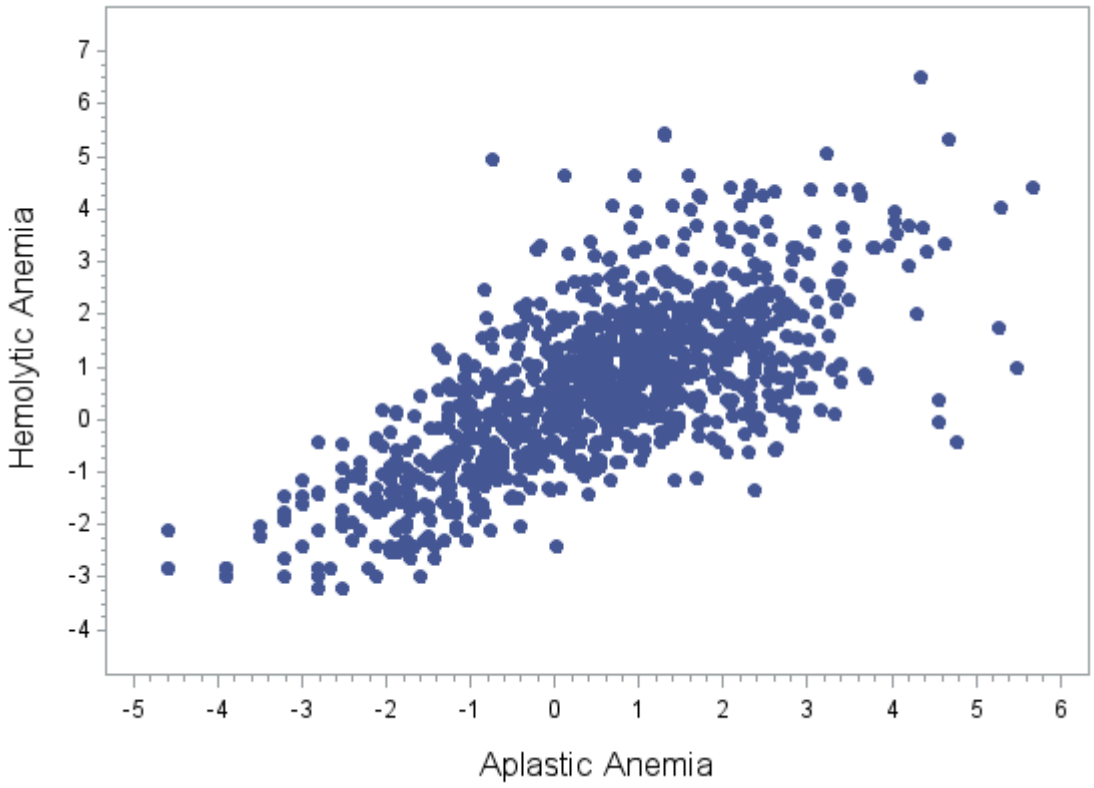


METHYLDOPA





Comparing All DME’s



Summary Statistics

Counts = 1043

Correlation Coefficient = 0.698

Pairwise Analysis of All DME's

- We have 34 DME's in the system currently
- There are: 33*34/2=561 pairwise comparisons
- Sort by Pearson's correlation coefficient in descending order

Pairwise Analysis of All DME's (Top 30)

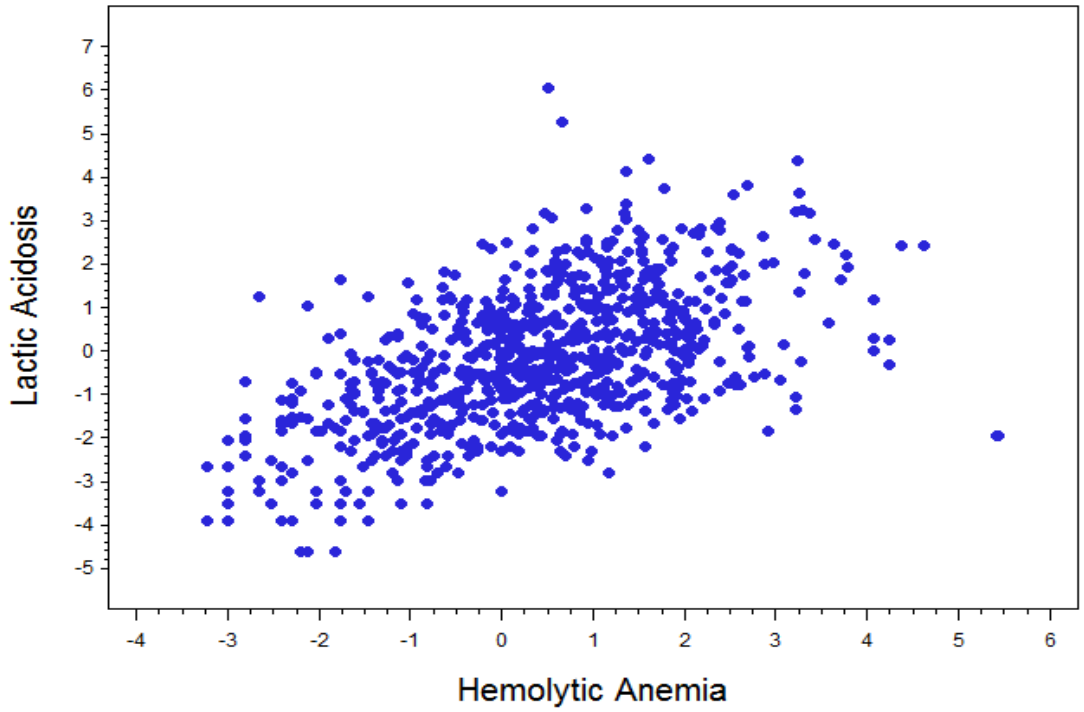
	DME1	DME2	No. of Common Substances	Correlation Coefficient
1	Stevens Johnson syndrome	Toxic epidemal necrolysis	1588	0.8857
2	Agranulocytosis	Pancytopenia	1499	0.8543
3	Aplastic anemia	Pancytopenia	1283	0.8281
4	Agranulocytosis	Aplastic anemia	1361	0.7995
5	Tosade de Pointes	Ventricular fibrillation	746	0.7951
6	Liver failure	Liver necrosis	1293	0.7722
7	Liver necrosis	Liver transplant	541	0.7601
8	Acute respiratory failure	Disseminated intravascular coagulation	1351	0.7545
9	Liver failure	Liver transplant	563	0.7534
10	Disseminated intravascular coagulation	Liver necrosis	1093	0.7433
11	Liver necrosis	Stevens Johnson syndrome	1249	0.7334
12	Disseminated intravascular coagulation	Pancytopenia	1191	0.7305
13	Haemolysis	Hemolytic anemia	892	0.7295
14	Liver necrosis	Toxic epidemal necrolysis	1219	0.7235
15	Neuroleptic malignant syndrome	Serotonin syndrome	457	0.7174
16	Liver necrosis	Rhabdomyolysis	1185	0.7148
17	Aplastic anemia	Disseminated intravascular coagulation	1119	0.7134
18	Disseminated intravascular coagulation	Liver failure	1256	0.7082
19	Pancytopenia	Renal failure	1597	0.7054
20	Aplastic anemia	Hemolytic anemia	1042	0.6979
21	Endotoxic shock confirmed or suspected	Product infectious disease transmission	66	0.6899
22	Haemolysis	TTP	566	0.6827
23	Acute respiratory failure	Renal failure	1922	0.6787
24	Disseminated intravascular coagulation	TTP	617	0.6787
25	Acute respiratory failure	Liver failure	1572	0.6754
26	Hemolytic anemia	TTP	606	0.6701
27	Disseminated intravascular coagulation	Toxic epidemal necrolysis	1177	0.6684
28	Agranulocytosis	Disseminated intravascular coagulation	1258	0.6682
29	Liver failure	Pancytopenia	1380	0.6671
30	Disseminated intravascular coagulation	Haemolysis	880	0.6651

Pairwise Analysis of All DME's (Bottom 30)

	DME1	DME2	No. of Common Substances	Correlation Coefficient
531	Blind	Suicide	985	0.1467
532	Acute respiratory failure	ALS Amyotrophic lateral sclerosis	370	0.1440
533	Pancytopenia	Product infectious disease transmission	300	0.1426
534	ALS Amyotrophic lateral sclerosis	Pulmonary hypertension	352	0.1416
535	ALS Amyotrophic lateral sclerosis	Seizure	348	0.1388
536	Haemolysis	Suicide	717	0.1369
537	Agranulocytosis	Suicide	1062	0.1360
538	Congenital anomalies	Renal failure	853	0.1349
539	Agranulocytosis	Product infectious disease transmission	315	0.1345
540	Anaphylaxis and anaphylactoid reactions	PML Progressive multifocal leukoencephalopathy	299	0.1345
541	ALS Amyotrophic lateral sclerosis	Blind	363	0.1267
542	Neuroleptic malignant syndrome	TTP	316	0.1235
543	Congenital anomalies	Pulmonary fibrosis	586	0.1233
544	PML Progressive multifocal leukoencephalopathy	Rhabdomyolysis	284	0.1205
545	Product infectious disease transmission	Renal failure	354	0.1075
546	Neuroleptic malignant syndrome	Pulmonary fibrosis	431	0.1049
547	Serotonin syndrome	TTP	352	0.1015
548	Colitis ischaemic	Suicide	714	0.1002
549	Aplastic anemia	Suicide	921	0.0706
550	Liver transplant	Suicide	475	0.0696
551	Pulmonary hypertension	Suicide	865	0.0555
552	Pulmonary fibrosis	Serotonin syndrome	501	0.0427
553	Pancytopenia	Suicide	984	0.0389
554	ALS Amyotrophic lateral sclerosis	Endotoxic shock confirmed or suspected	353	0.0380
555	PML Progressive multifocal leukoencephalopathy	Product infectious disease transmission	92	-0.0062
556	PML Progressive multifocal leukoencephalopathy	Serotonin syndrome	149	-0.0232
557	Pulmonary fibrosis	Suicide	777	-0.0311
558	Suicide	TTP	513	-0.0335
559	Neuroleptic malignant syndrome	PML Progressive multifocal leukoencephalopathy	131	-0.0552
560	Endotoxic shock confirmed or suspected	Suicide	107	-0.0705
561	PML Progressive multifocal leukoencephalopathy	Suicide	248	-0.1272

Effect of Different Classes of Substances

Lactic Acidosis vs. Hemolytic Anemia
All Substances

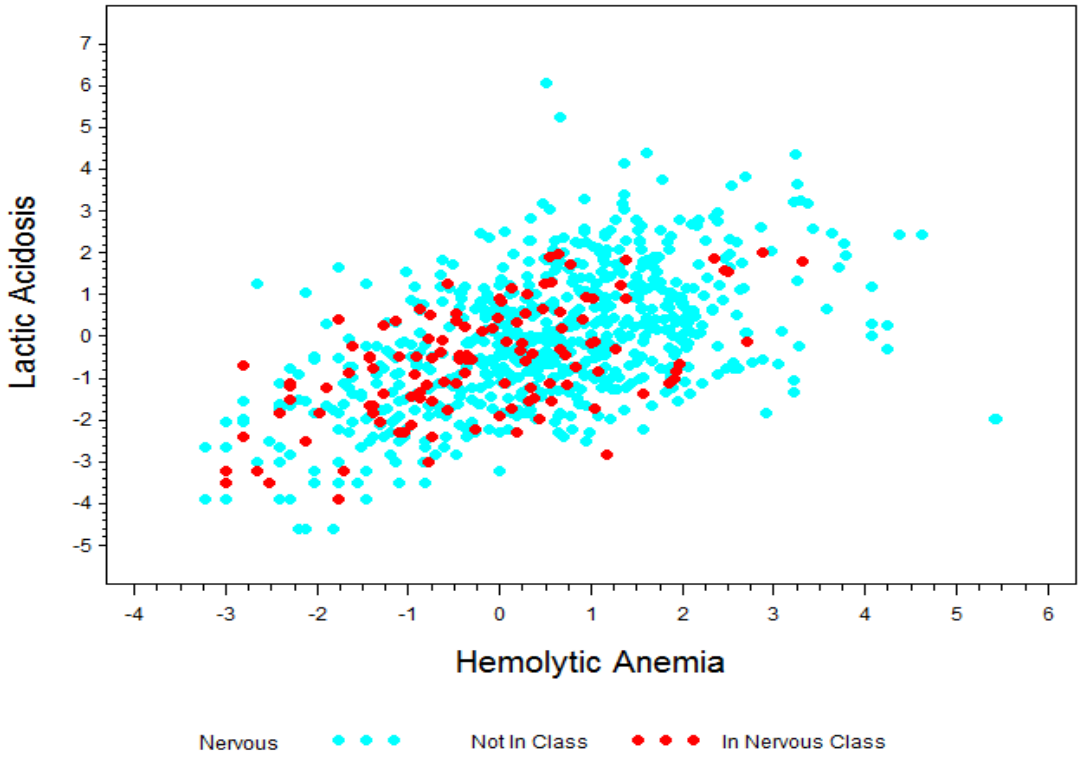


Summary Statistics

Counts = 874

Cor = 0.556

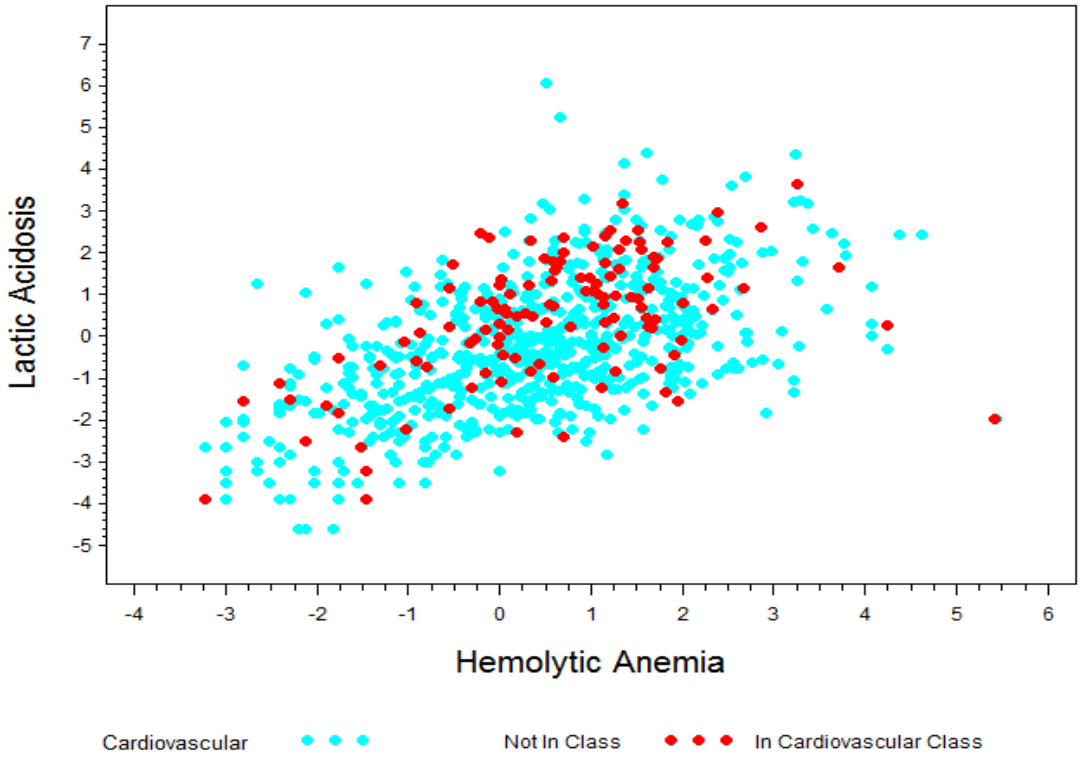
Lactic Acidosis vs. Hemolytic Anemia Nervous Class



All Substances
Counts = 874
Correlation = 0.556

Nervous Class
Counts = 120
Correlation = 0.560

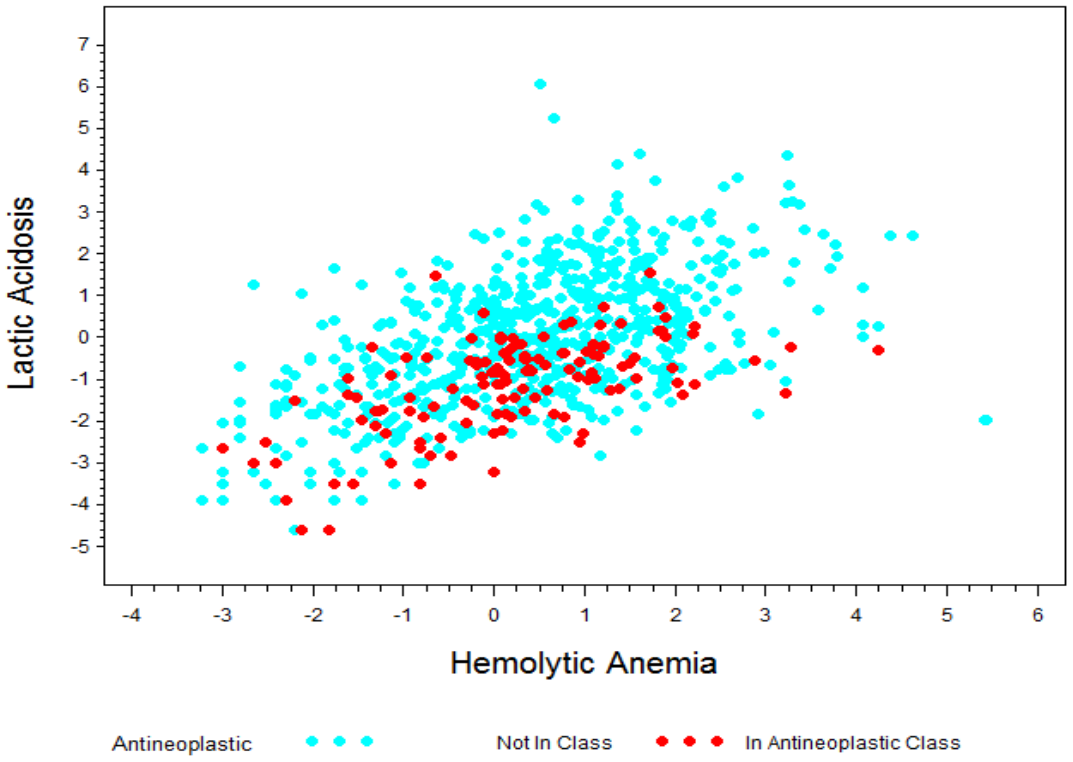
Lactic Acidosis vs. Hemolytic Anemia Cardiovascular Class



All Substances
Counts = 874
Correlation = 0.556

Cardiovascular Class
Counts = 122
Correlation = 0.494

Lactic Acidosis vs. Hemolytic Anemia Antineoplastic Class



All Substances
Counts = 874
Correlation = 0.556

Antineoplastic Class
Counts = 133
Correlation = 0.594

Diabetes Drugs

Diabetes Drugs

- There are 55 substances in G-SRS which are related to diabetes and their relationships to DME Reactions

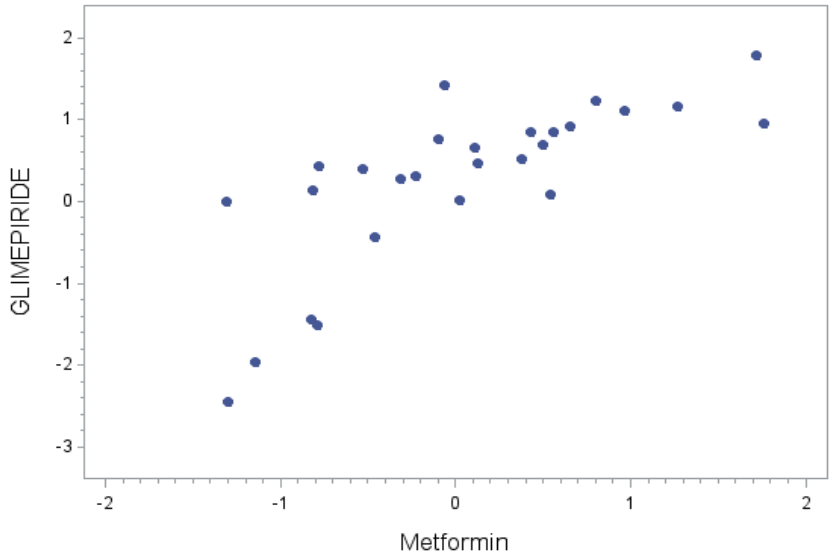
- We investigated the common DME reactions associated with **Metformin** versus the other 54 substances to see whether there is any particular pattern that is specific to Metformin but not the others.

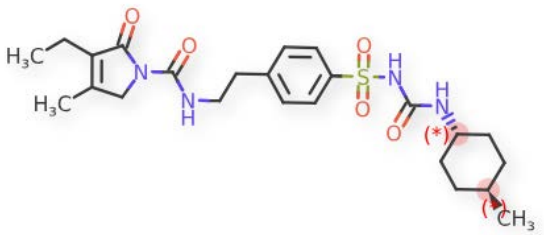
METFORMIN Vs. All 54 Substances

	DRUGS	# Common DME Reactions	Correlation Coefficient
1	GLIMEPIRIDE	27	0.7547
2	PIOGLITAZONE	29	0.7374
3	ALBIGLUTIDE	11	0.6651
4	ACETOHEXAMIDE	11	0.6651
5	SITAGLIPTIN	28	0.6268
6	ROSIGLITAZONE	29	0.5422
7	MIGLITOL	29	0.5422
8	LIRAGLUTIDE	24	0.5068
9	EMPAGLIFLOZIN	23	0.4963
10	GLIPIZIDE	28	0.4933
11	EXENATIDE	27	0.4631
12	GLYBURIDE	28	0.4531
13	PRAMLINTIDE	12	0.4346
14	TOLRESTAT	12	0.4346
15	GLIBORNURIDE	12	0.4346
16	LINAGLIPTIN	22	0.4322
17	SIMVASTATIN	31	0.4102
18	CANAGLIFLOZIN	31	0.4102
19	SAXAGLIPTIN ANHY	31	0.4102
20	SAXAGLIPTIN MONO	31	0.4102
21	INSULIN GLARGINE	29	0.3587
22	INSULIN DEGLUDEC	16	0.3126
23	INSULIN ASPART	27	0.2766
24	VOGLIBOSE	27	0.2766
25	BUFORMIN	27	0.2766
26	VILDAGLIPTIN	22	0.2678
27	INSULIN LISPRO	30	0.2350
28	GLICLAZIDE	28	0.2310
29	METAHEXAMIDE	28	0.2310
30	MITIGLINIDE	28	0.2310
31	GLISOXEPIDE	28	0.2310
32	GUAR GUM	28	0.2310
33	GLYMIDINE	28	0.2310
34	GLIQUIDONE	28	0.2310

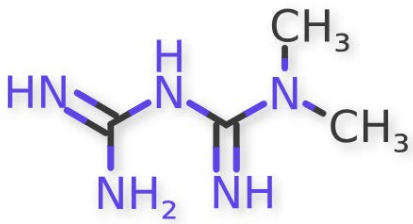
	Drugs	# Common DME Reactions	Correlation Coefficient
35	CARBUTAMIDE	28	0.2310
36	GEMIGLIPTIN	28	0.2310
37	NATEGLINIDE	23	0.2201
38	TROGLITAZONE	27	0.1897
39	TOLBUTAMIDE	27	0.1897
40	DULAGLUTIDE	20	0.1754
41	INSULIN HUMAN	28	0.1575
42	REPAGLINIDE	24	0.1482
43	PHENFORMIN	24	0.1482
44	INSULIN BEEF	24	0.1482
45	BENFLUOREX	24	0.1482
46	DAPAGLIFLOZIN	25	0.1323
47	INSULIN DETEMIR	21	0.1209
48	INSULIN GLULISIN	21	0.1209
49	ALOGLIPTIN	19	0.0966
50	TOLAZAMIDE	14	0.0754
51	ACARBOSE	23	0.0161
52	LIXISENATIDE	23	0.0161
53	INSULIN PORK	17	-0.0329
54	CHLORPROPAMIDE	22	-0.4475

PRR Values in LOG Scale for
Common DME Reactions Between GLIMEPIRIDE and METFORMIN
Correlation = 0.7547, N=27



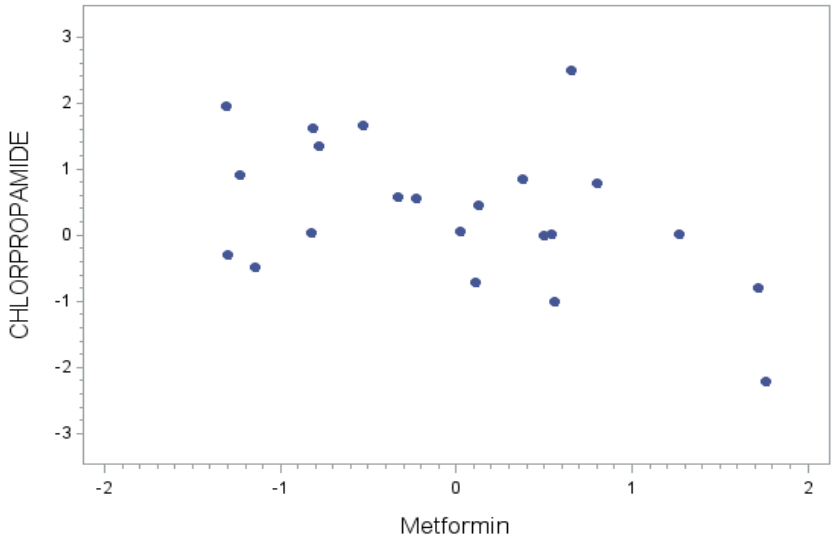


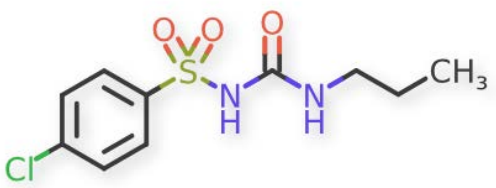
GLIMEPIRIDE



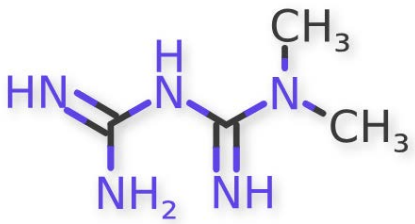
METFORMIN

PRR Values in LOG Scale for
Common DME Reactions Between CHLORPROPAMIDE and METFORMIN
Correlation = - 0.4475, N=22





CHLORPROPAMIDE



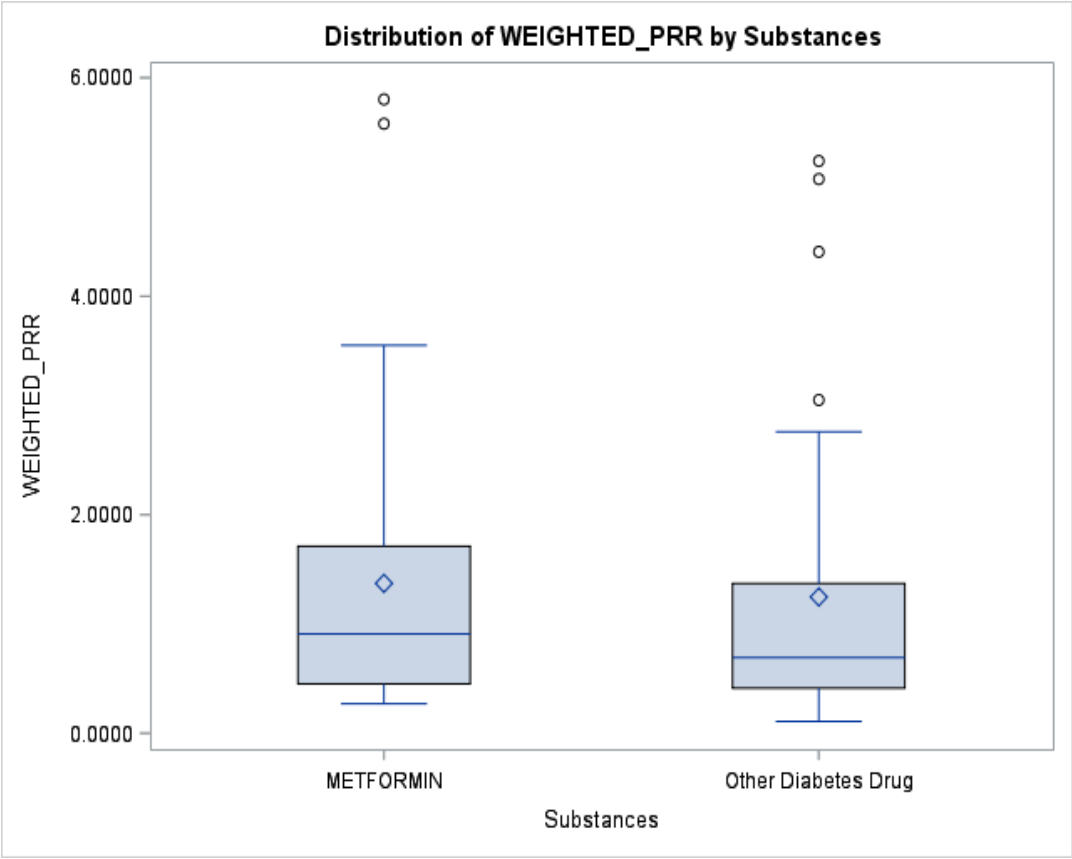
METFORMIN

Diabetes Drugs

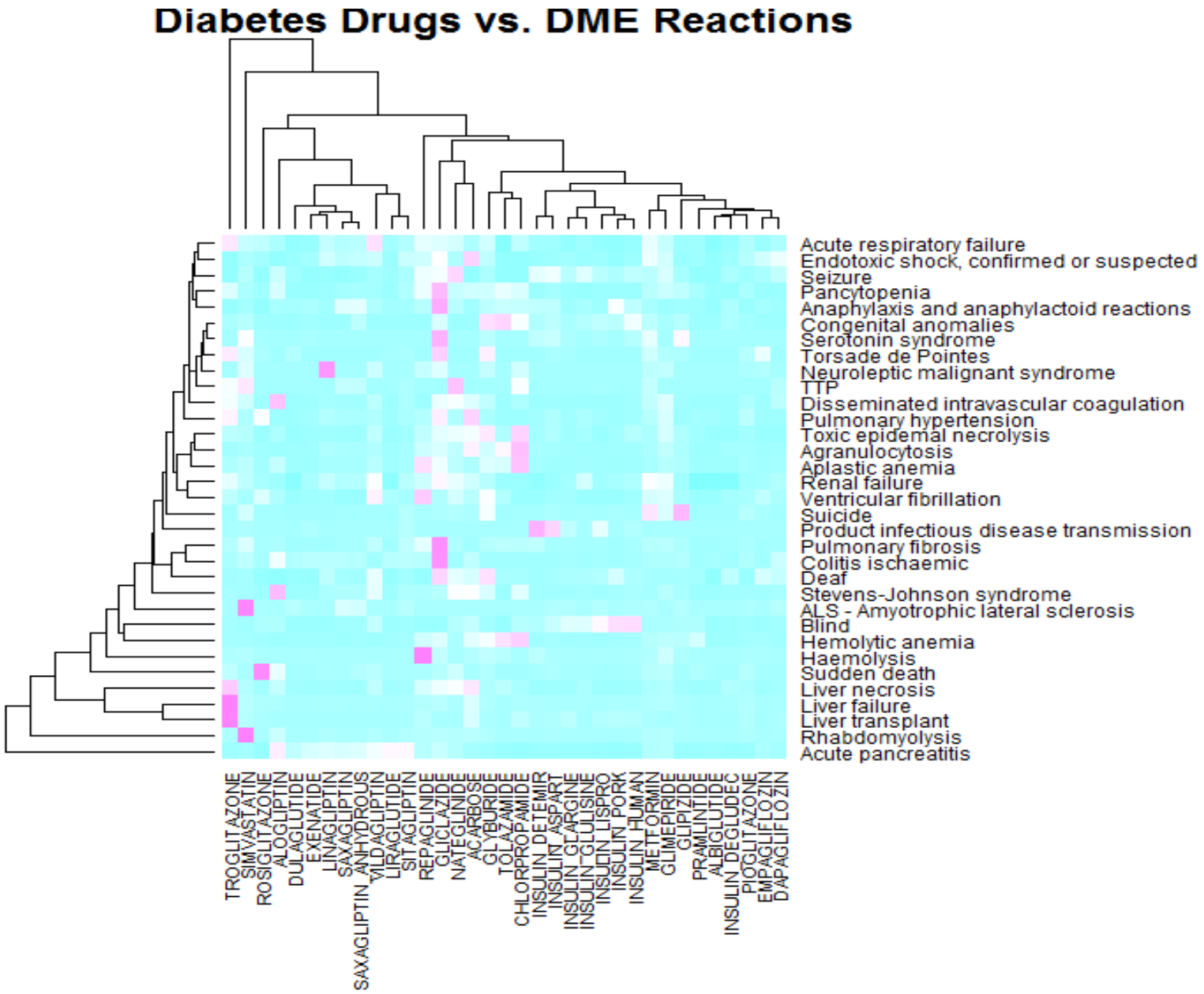
- Only 35 substances have CASE_COUNT > 1000, for reliable PRR values.

- For these substances we have 33 DME Reactions available in GSRS.

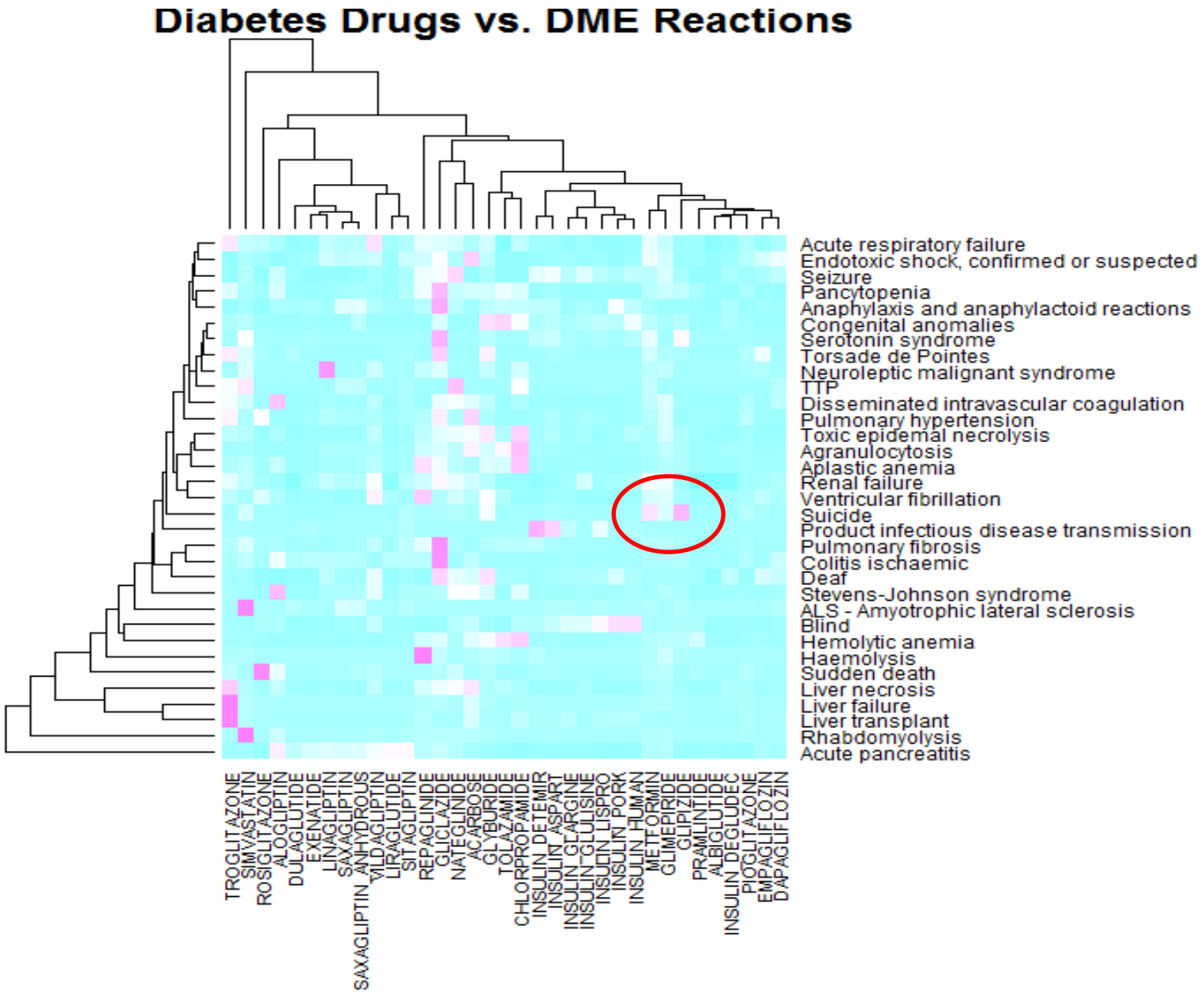
Distribution Difference Between METFORMIN and All Other Substances Combined



All Substances Associated With Diabetes

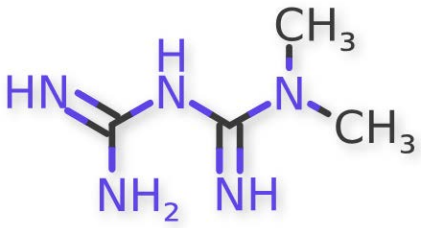


All Substances Associated With Diabetes

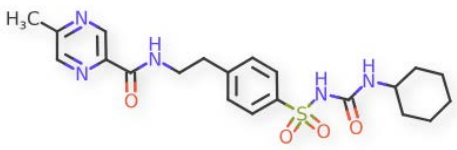


Suicide

Metformin



Glipizide

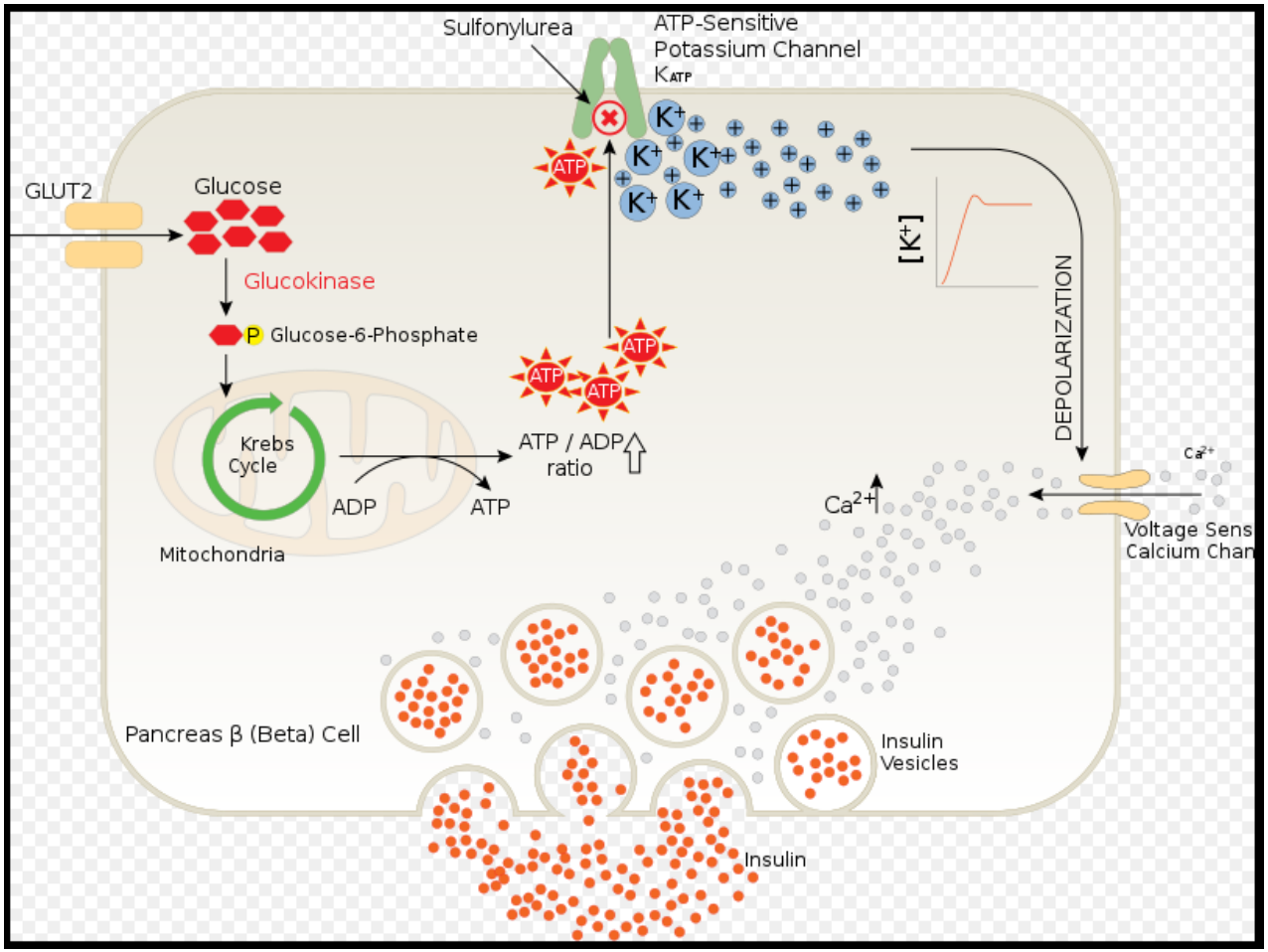


Analysis
at
the PT-Term Level

Sulfonylurea Drugs

- We are interested in diabetes drugs that have the same target to determine whether they are associated with the same AEs.
- Sulfonylurea drugs are special types of antidiabetic drugs that have the same target.
- They act by increasing insulin release from the beta cells in the pancreas.

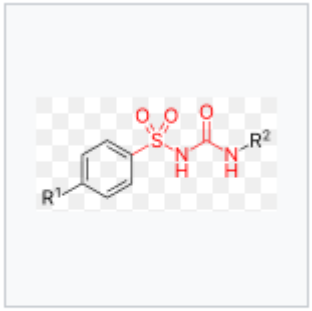
Sulfonylurea Drugs



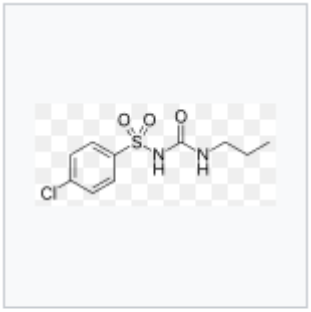
Sulfonylurea Drugs

- There are 5 sulfonylurea drugs found in GSRS which have CASE_COUNT ≥ 1000 and corresponding AEs with PT_TERM ≥ 5:
  - CHLORPROPAMIDE
  - GLICLAZIDE
  - GLIPIZIDE
  - GLYBURIDE
  - TOLAZAMIDE

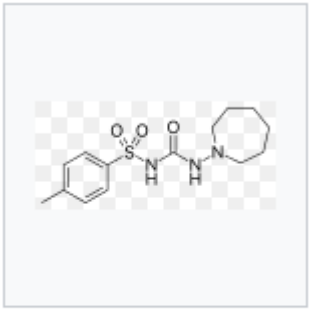
Sulfonylurea Drugs



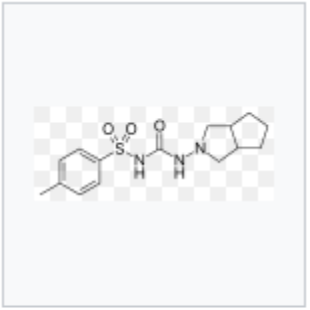
Sulfonylurea group highlighted in (red)



Chlorpropamide (1st generation)

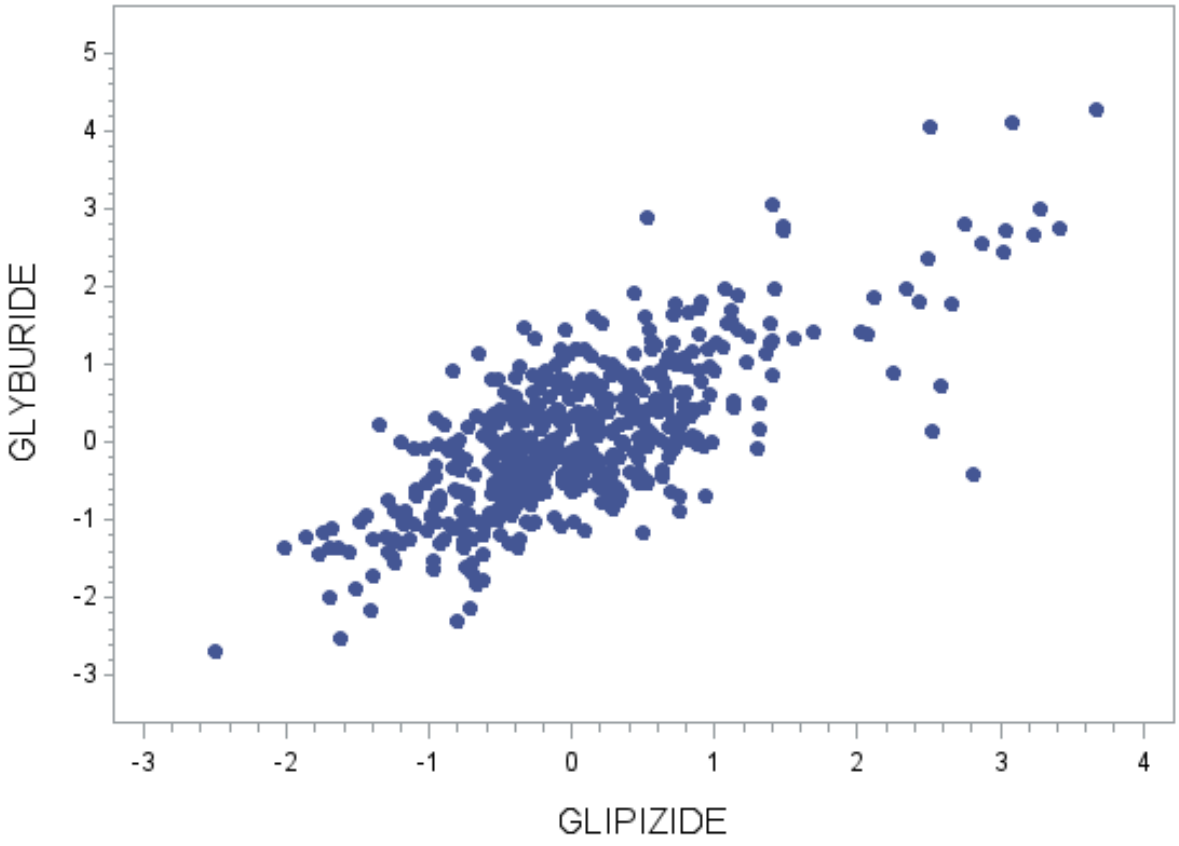


Tolazamide (1st generation)



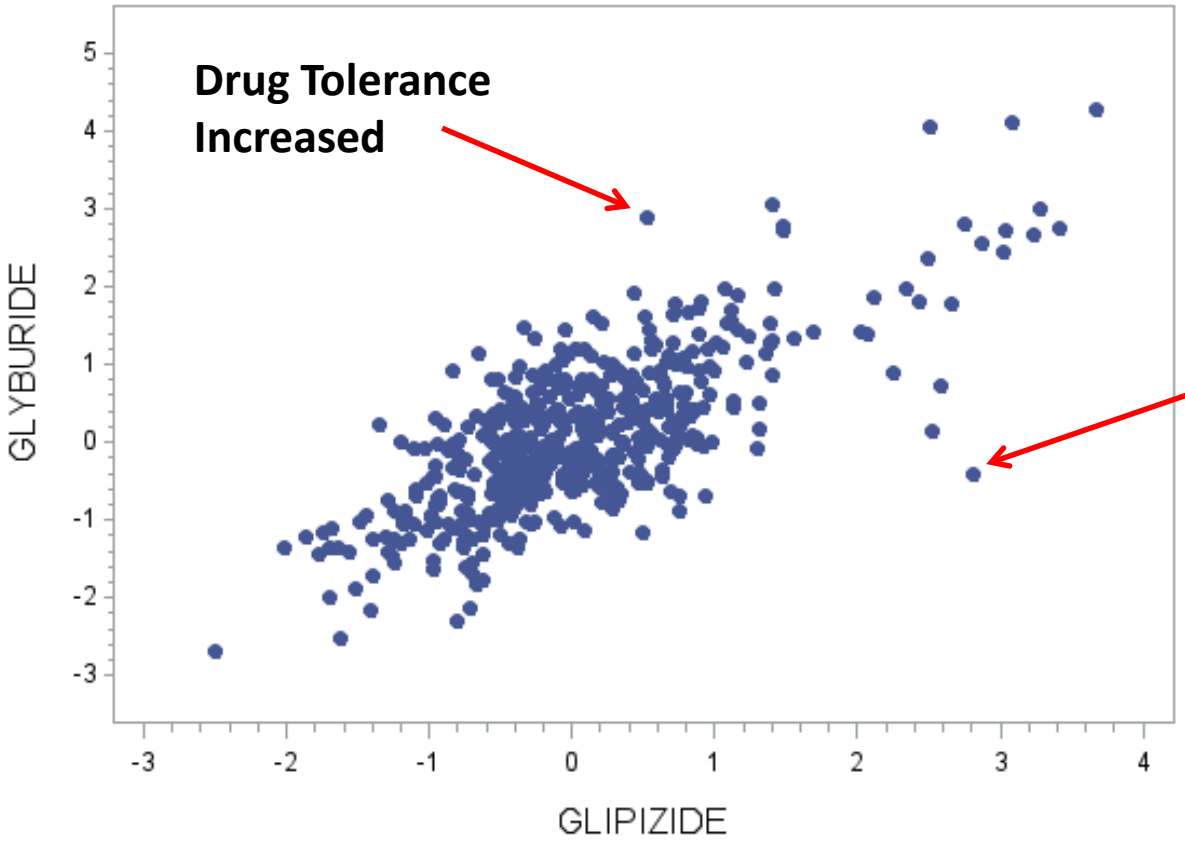
Gliclazide (2nd generation)

GLYBURIE vs. GLIPIZIDE



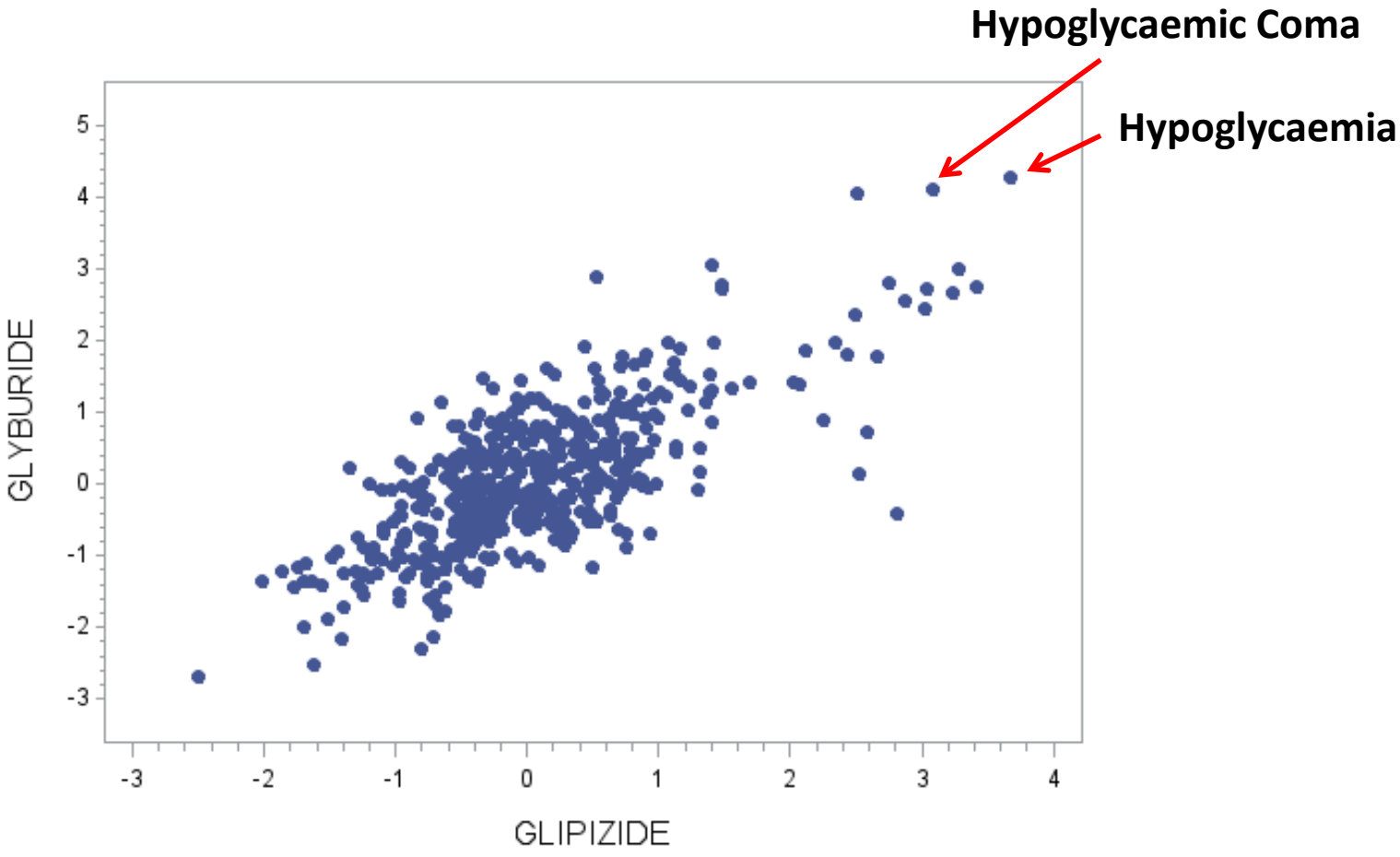
GLYBURIE vs. GLIPIZIDE

Outliers



GLYBURIE vs. GLIPIZIDE

Common AEs



PT-Terms of the Top 5% PRR -- Sulfonylurea Drugs

	GLICLAZIDE (N=2827)	PT COUNT
1	HYPOGLYCAEMIA	548
2	LACTIC ACIDOSIS	152
3	METABOLIC ACIDOSIS	119
4	DIABETES MELLITUS INADEQUATE CONTROL	117
5	HYPERKALAEMIA	95
6	HYPOGLYCAEMIC COMA	63
7	PANCREATIC CARCINOMA	41
8	PEMPHIGOID	38
9	HYPERLACTACIDAEMIA	33
10	ACIDOSIS	31
11	DIABETIC METABOLIC DECOMPENSATION	31
12	BRADYPHRENIA	23
13	HEPATITIS CHOLESTATIC	16
14	GASTROINTESTINAL MOTILITY DISORDER	15
15	VOMITING PROJECTILE	15
16	CARDIOACTIVE DRUG LEVEL INCREASED	14
17	DISTRIBUTIVE SHOCK	14
18	HAEMOGLOBIN INCREASED	14
19	HAND DEFORMITY	14
20	JOINT NOISE	14
21	SCOLIOSIS	14
22	BRONCHIECTASIS	13
23	POISONING DELIBERATE	13
24	PULSE ABNORMAL	13
25	HEPATITIS FULMINANT	12
26	LICHEN PLANUS	12
27	NORMOCHROMIC NORMOCYTIC ANAEMIA	12
28	IDIOPATHIC PULMONARY FIBROSIS	11
29	URINARY TRACT DISCOMFORT	10
30	BRADYKINESIA	8
31	DIABETIC HYPEROSMOLAR COMA	8
32	SLEEP TERROR	8
33	FOETAL DISORDER	7
34	JEALOUS DELUSION	7
35	RIGHT VENTRICULAR DYSFUNCTION	7
36	ACUTE LUNG INJURY	6
37	IMPULSE-CONTROL DISORDER	6
38	INHIBITORY DRUG INTERACTION	6
39	ANAEMIA VITAMIN B12 DEFICIENCY	5
40	BODY MASS INDEX DECREASED	5
41	CALCIPHYLAXIS	5
42	DIABETIC KETOSIS	5
43	DIABETIC ULCER	5
44	HALO VISION	5
45	HYPOGLYCAEMIA NEONATAL	5
46	ORBITAL OEDEMA	5
47	SLOW RESPONSE TO STIMULI	5

	GLYBURIDE (N=11205)	PT COUNT
1	HYPOGLYCAEMIA	2671
2	LACTIC ACIDOSIS	244
3	DIABETES MELLITUS INADEQUATE CONTROL	168
4	HYPOGLYCAEMIC COMA	114
5	DRUG TOLERANCE INCREASED	70
6	HYPOGLYCAEMIC UNCONSCIOUSNESS	29
7	SHOCK HYPOGLYCAEMIC	25
8	HYPOGLYCAEMIC ENCEPHALOPATHY	18
9	MUCOSAL EROSION	17
10	CONGENITAL MUSCULOSKELETAL ANOMALY	13
11	OTITIS EXTERNA	13
12	QUADRIPARESIS	13
13	MACROSOMIA	12
14	METABOLIC ALKALOSIS	12
15	SCROTAL OEDEMA	12
16	NEPHROCALCINOSIS	11
17	GRANULOMATOUS LIVER DISEASE	9
18	PULMONARY HYPOPLASIA	9
19	DRUG CLEARANCE DECREASED	8
20	SPINE MALFORMATION	8
21	MICROALBUMINURIA	7
22	BLOOD GLUCOSE	6
23	BLOOD ZINC DECREASED	6
24	TYMPANIC MEMBRANE DISORDER	6
25	HYPERINSULINAEMIA	5
26	INSULIN C-PEPTIDE INCREASED	5
27	PLATELET COUNT NORMAL	5
28	RIB HYPOPLASIA	5
29	TRANSVERSE PRESENTATION	5

	GLIPIZIDE (N=9980)	PT COUNT
1	HYPOGLYCAEMIA	1358
2	HYPERGLYCAEMIA	705
3	BLOOD GLUCOSE DECREASED	452
4	DIABETES MELLITUS INADEQUATE CONTROL	287
5	GLYCOSYLATED HAEMOGLOBIN INCREASED	195
6	BLOOD GLUCOSE FLUCTUATION	144
7	MEDICATION RESIDUE PRESENT	110
8	HYPOGLYCAEMIC COMA	38
9	GLUCOSE TOLERANCE DECREASED	13
10	ACCIDENTAL POISONING	8
11	BLOOD GLUCOSE	7
12	MEDICAL DEVICE SITE INFECTION	6
13	MICROALBUMINURIA	6
14	STOOL ANALYSIS ABNORMAL	6

	CHLORPROPAMIDE (N=1904)	PT COUNT
1	HYPOGLYCAEMIA	222
2	INAPPROPRIATE ANTIDIURETIC HORMONE SECRETION	31
3	JAUNDICE CHOLESTATIC	31
4	CORONARY ARTERY BYPASS	21
5	CATARACT OPERATION	11
6	LEG AMPUTATION	10
7	TOE AMPUTATION	9
8	VENOUS OCCLUSION	9
9	DIABETIC COMPLICATION	8
10	DIABETIC COMA	7
11	ANGIOPLASTY	6

	TOLAZAMIDE (N=1223)	PT COUNT
1	HYPERGLYCAEMIA	137
2	HYPOGLYCAEMIA	116
3	AMBLYOPIA	70
4	JAUNDICE CHOLESTATIC	15
5	INAPPROPRIATE ANTIDIURETIC HORMONE SECRETION	14
6	GANGRENE	11
7	KETOACIDOSIS	11
8	PATHOLOGICAL FRACTURE	10
9	GASTROINTESTINAL CARCINOMA	8

PT-Terms of the Top 5% PRR -- Sulfonylurea Drugs

- Notice that AMBLYOPIA is an AE with PT_COUNT of 70 for TOLAZAMIDE (N=1223)
- AMBLYOPIA also known as *lazy eye*, which is a vision development disorder in which one eye fails to achieve normal visual acuity; the vision of one of the eyes is reduced because the eye and the brain are not working together properly
- DAILYMED does not report it as an AE for TOLAZAMIDE

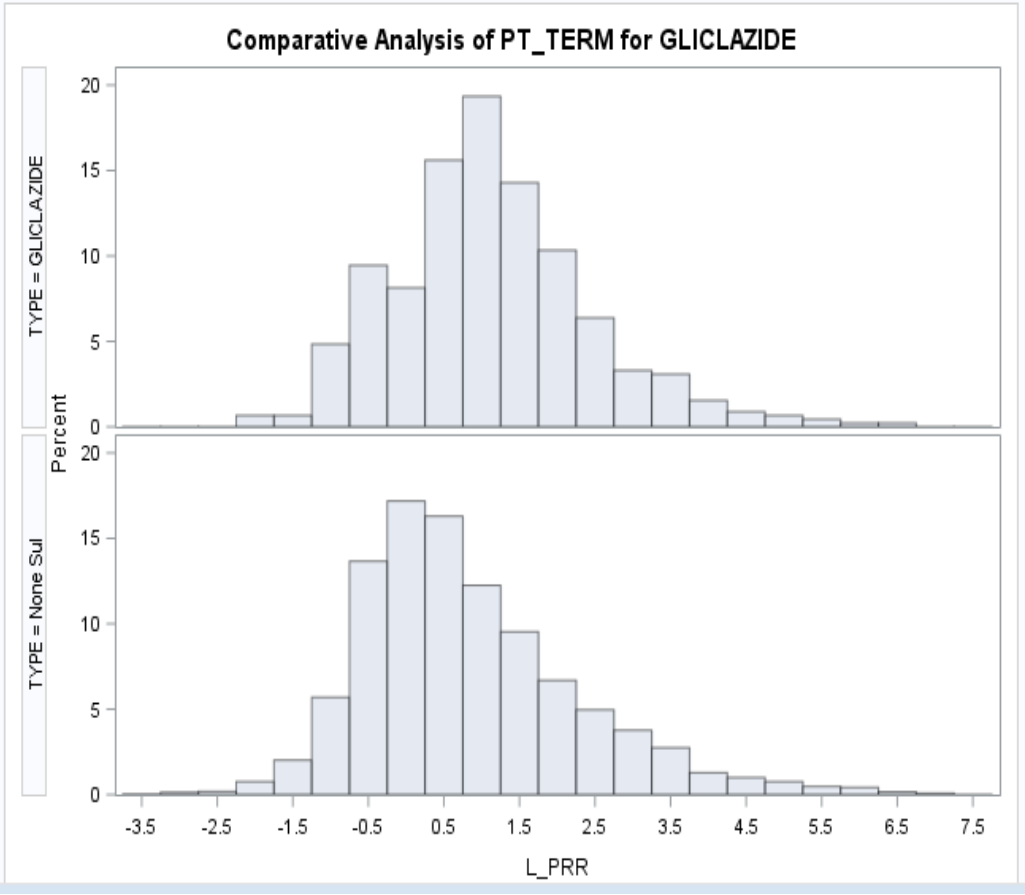
Sulfonylurea Drugs
vs.
Other Diabetes Drugs

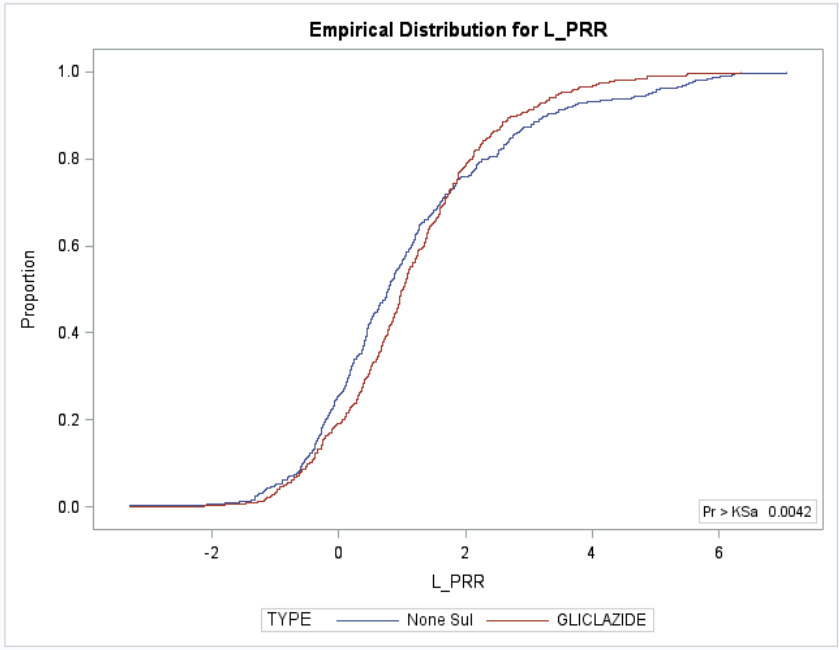
	Sulfonylurea Drugs
1	CHLORPROPAMIDE
2	GLICLAZIDE
3	GLIPIZIDE
4	GLYBURIDE
5	TOLAZAMIDE

Vs.

	None Sulfonylurea
1	ACARBOSE
2	ALBIGLUTIDE
3	ALOGLIPTIN
4	DAPAGLIFLOZIN
5	DULAGLUTIDE
6	EMPAGLIFLOZIN
7	EXENATIDE
8	GLIMEPIRIDE
9	INSULIN ASPART
10	INSULIN DEGLUDEC
11	INSULIN DETEMIR
12	INSULIN GLARGINE
13	INSULIN GLULISINE
14	INSULIN HUMAN
15	INSULIN LISPRO
16	INSULIN PORK
17	LINAGLIPTIN
18	LIRAGLUTIDE
19	METFORMIN
20	NATEGLINIDE
21	PIOGLITAZONE
22	PRAMLINTIDE
23	REPAGLINIDE
24	ROSIGLITAZONE
25	SAXAGLIPTIN
26	SAXAGLIPTIN ANHYDROUS
27	SIMVASTATIN
28	SITAGLIPTIN
29	TROGLITAZONE
30	VILDAGLIPTIN

GLICLAZIDE (N=455) versus 30 Non-Sulfonylurea Diabetes Drugs



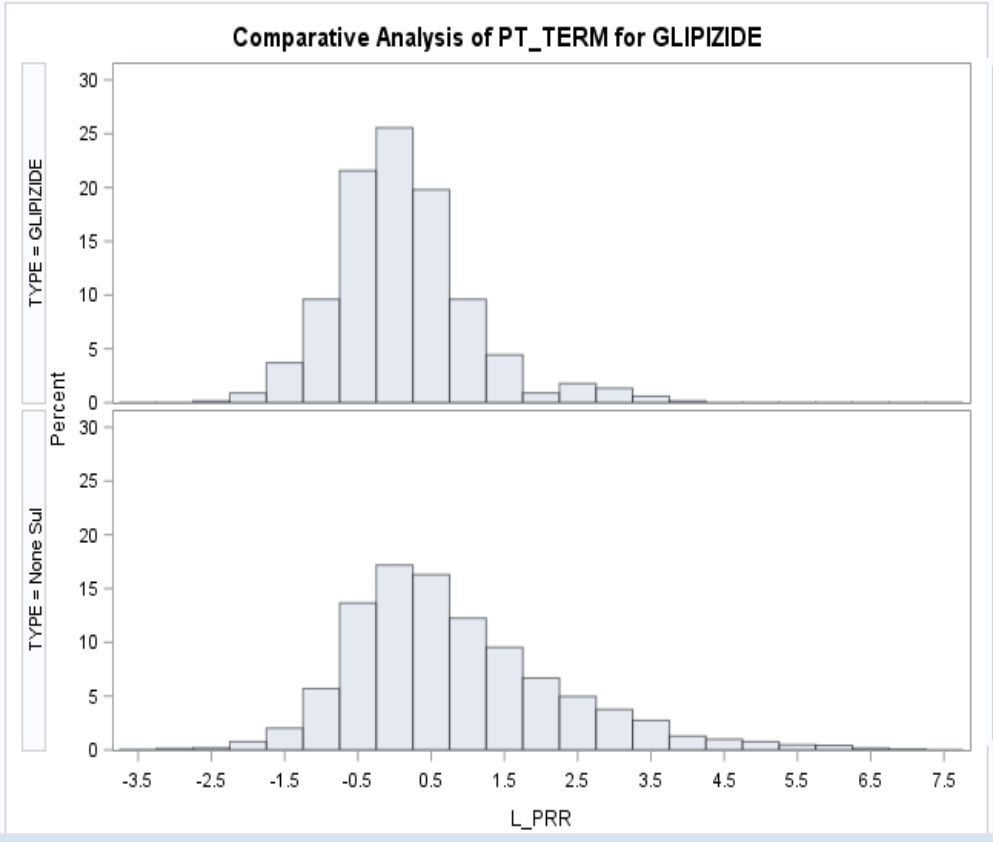


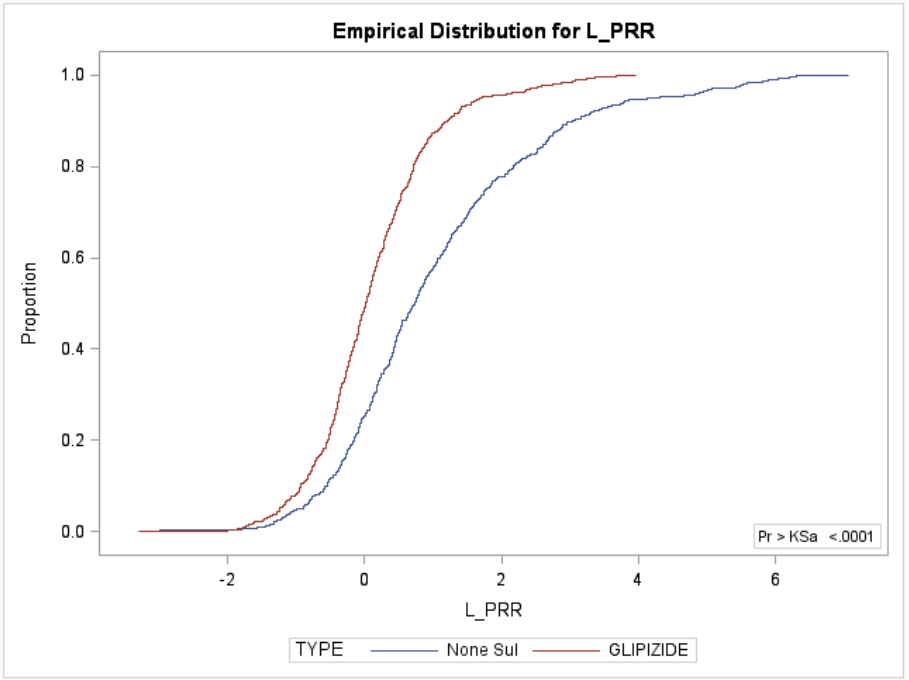
Sulfonylurea Drugs > Other 30 Diabetes Drugs -- by 50

GLICLAZIDE (N=455)

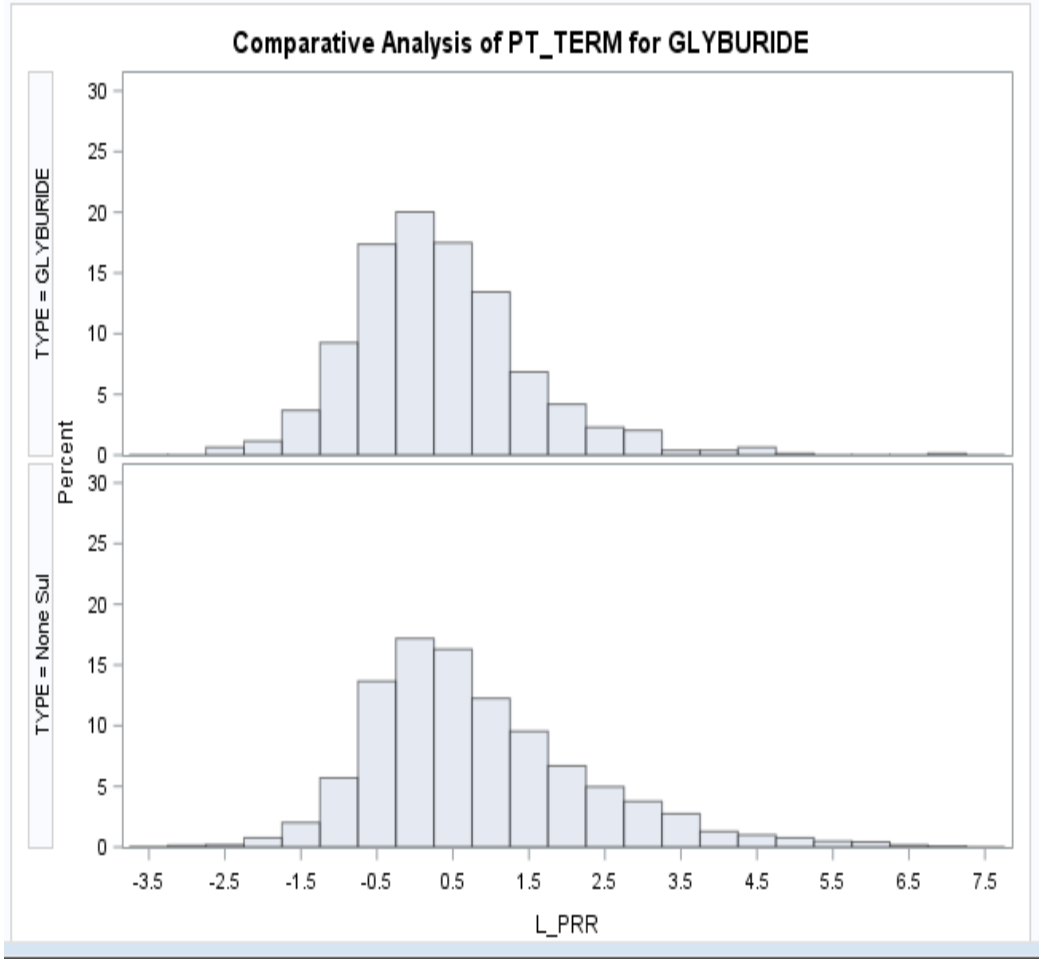
	PT_TERM	NONE SUL	GLICLAZIDE
1	DIABETIC METABOLIC DECOMPENSATION	36	418
2	DISTRIBUTIVE SHOCK	24	248
3	DIABETIC KETOSIS	40	238
4	JEALOUS DELUSION	6	166
5	HYPOGLYCAEMIC COMA	26	130
6	BODY MASS INDEX DECREASED	7	108
7	HYPERLACTACIDAEMIA	35	129
8	DIABETIC HYPEROSMOLAR COMA	5	84
9	RIGHT VENTRICULAR DYSFUNCTION	3	77
10	ACUTE LUNG INJURY	3	62
11	ORBITAL OEDEMA	4	61
12	ANAEMIA VITAMIN B12 DEFICIENCY	16	71
13	CARDIOACTIVE DRUG LEVEL INCREASED	1	53

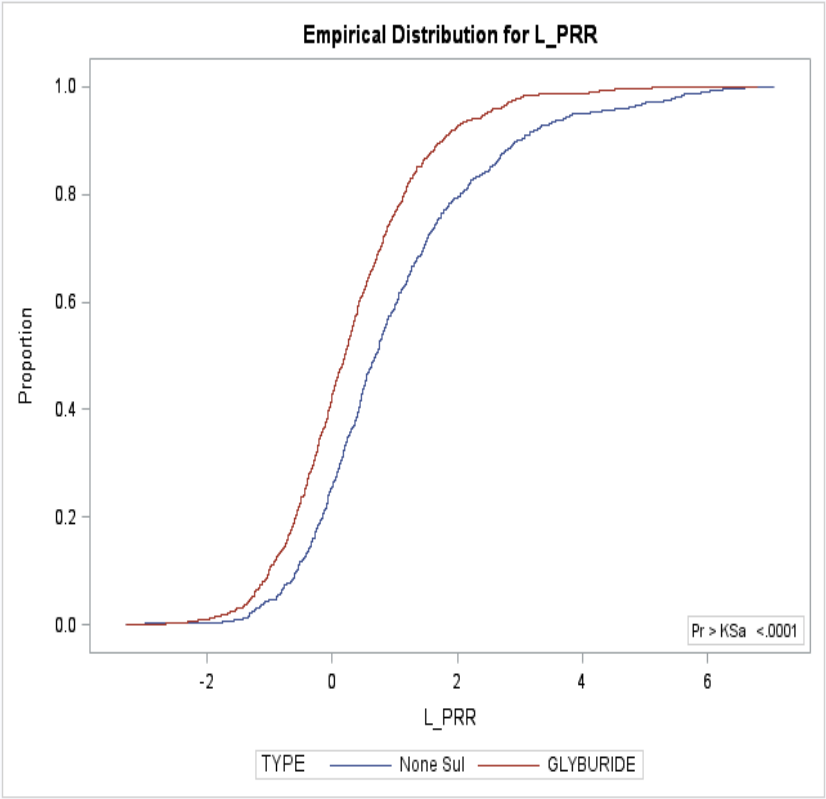
GLIPIZIDE (N=677) versus 30 Non-Sulfonylurea Diabetes Drugs





GLYBURIDE (N=789) versus 30 Non-Sulfonylurea Diabetes Drugs





Sulfonylurea Drugs > Other 30 Diabetes Drugs -- by 50

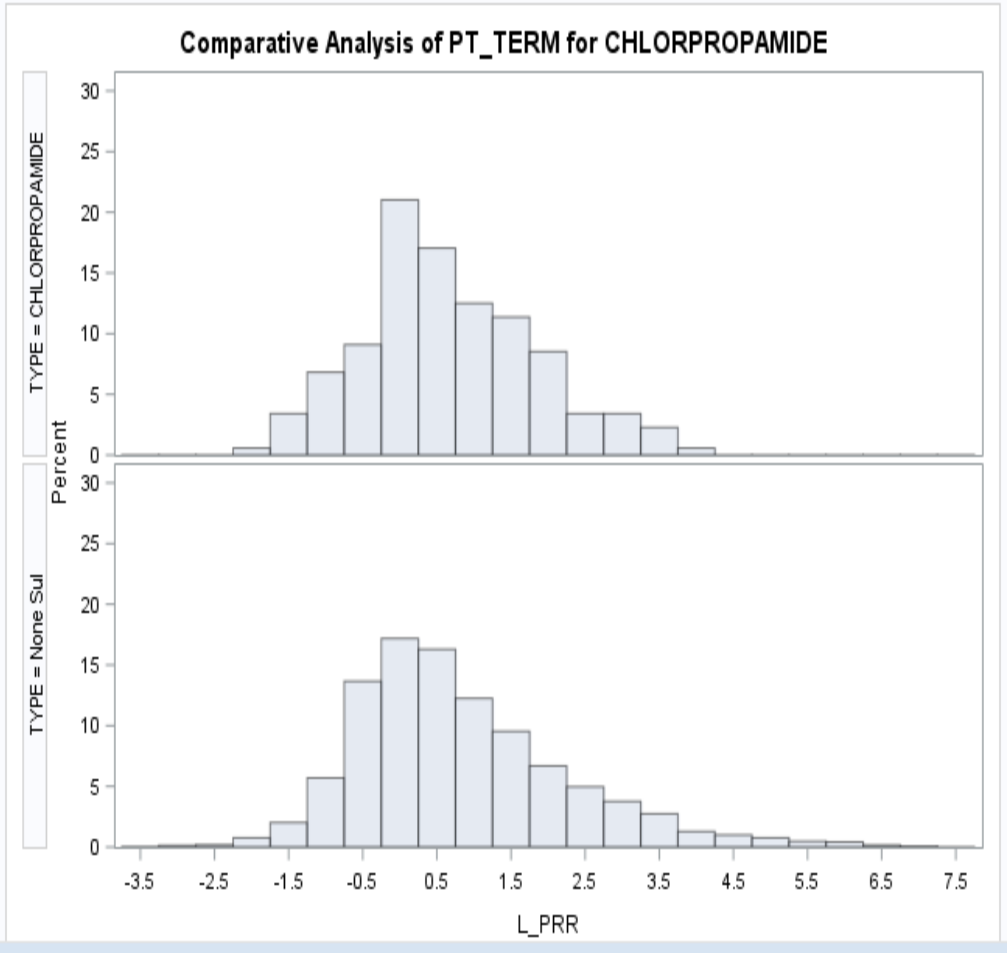
GLICLAZIDE (N=455)

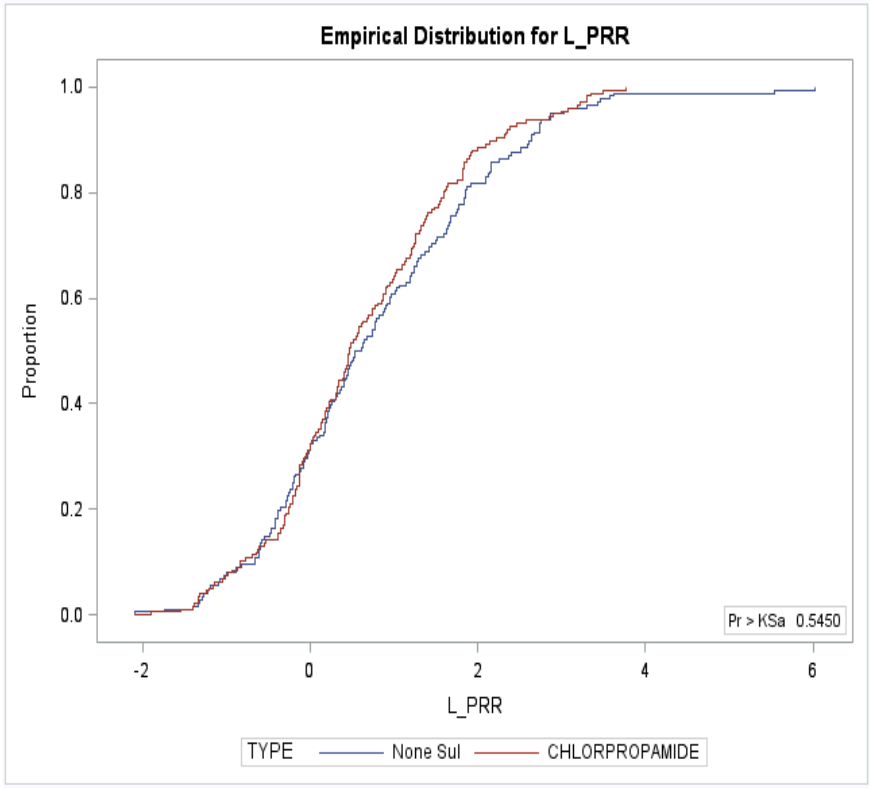
	PT_TERM	NONE SUL	GLICLAZIDE
1	DIABETIC METABOLIC DECOMPENSATION	36	418
2	DISTRIBUTIVE SHOCK	24	248
3	DIABETIC KETOSIS	40	238
4	JEALOUS DELUSION	6	166
5	HYPOGLYCAEMIC COMA	26	130
6	BODY MASS INDEX DECREASED	7	108
7	HYPERLACTACIDAEMIA	35	129
8	DIABETIC HYPEROSMOLAR COMA	5	84
9	RIGHT VENTRICULAR DYSFUNCTION	3	77
10	ACUTE LUNG INJURY	3	62
11	ORBITAL OEDEMA	4	61
12	ANAEMIA VITAMIN B12 DEFICIENCY	16	71
13	CARDIOACTIVE DRUG LEVEL INCREASED	1	53

GLYBURIDE (N=789)

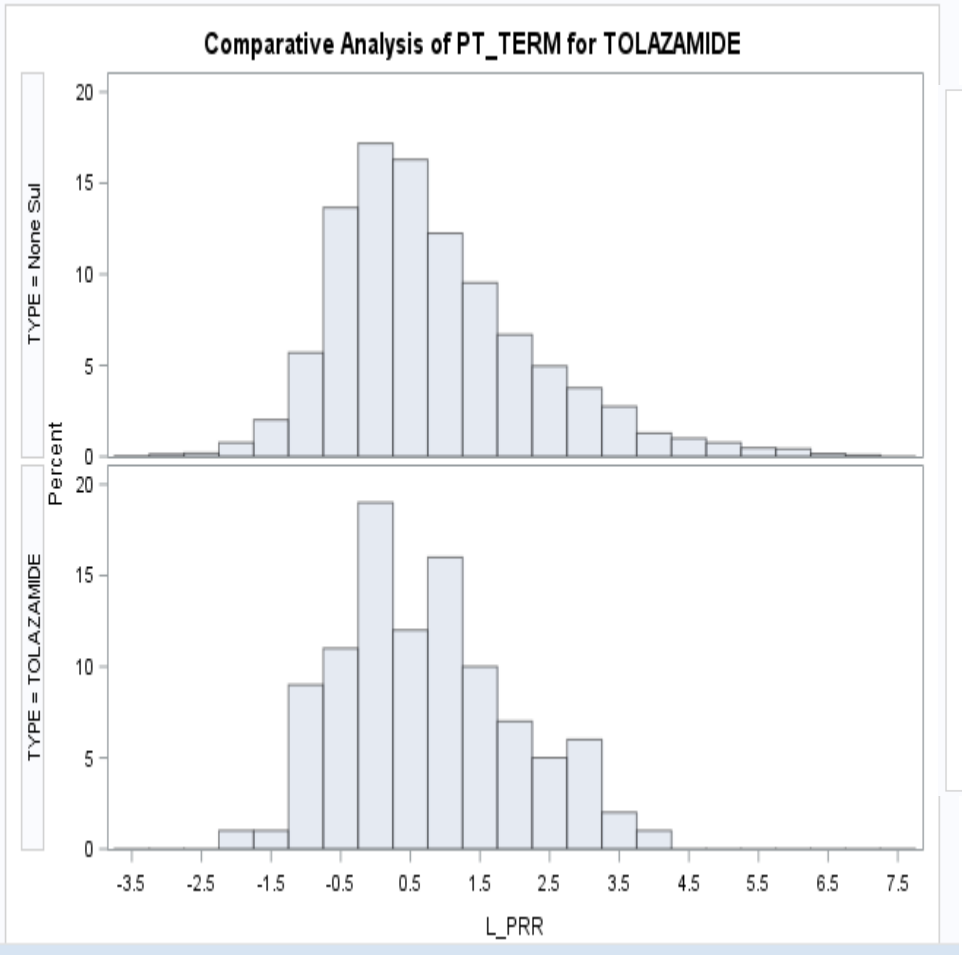
	PT_TERM	NONE SUL	GLYBURIDE
1	PLATELET COUNT NORMAL	170	892
2	RIB HYPOPLASIA	22	167
3	MACROSOMIA	18	91
4	BLOOD ZINC DECREASED	15	81
5	HYPOGLYCAEMIC ENCEPHALOPATHY	38	104
6	HYPOGLYCAEMIA	12	71

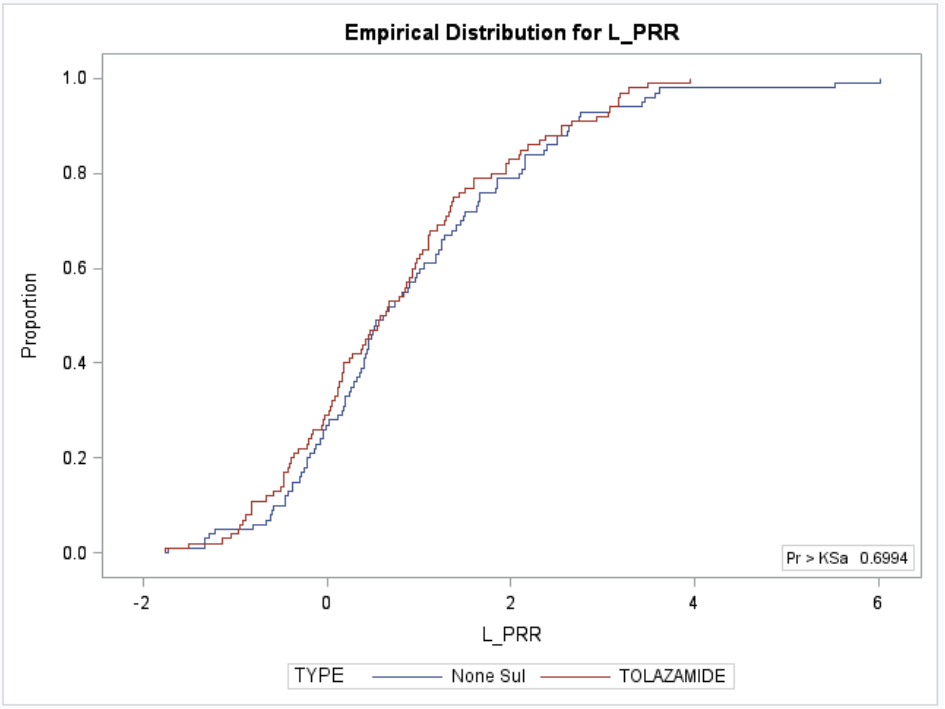
CHLORPROPAMIDE (N=176) versus 30 Non-Sulfonylurea Diabetes Drugs





TOLAZAMIDE (N=100) versus 30 Non-Sulfonylurea Diabetes Drugs





Sulfonylurea Drugs > Other 30 Diabetes Drugs -- by 50

GLICLAZIDE (N=455)

	PT_TERM	NONE SUL	GLICLAZIDE
1	DIABETIC METABOLIC DECOMPENSATION	36	418
2	DISTRIBUTIVE SHOCK	24	248
3	DIABETIC KETOSIS	40	238
4	JEALOUS DELUSION	6	166
5	HYPOGLYCAEMIC COMA	26	130
6	BODY MASS INDEX DECREASED	7	108
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13	CARDIOACTIVE DRUG LEVEL INCREASED	1	53

GLYBURIDE (N=789)

	PT_TERM	NONE SUL	GLYBURIDE
1	PLATELET COUNT NORMAL	170	892
2	RIB HYPOPLASIA	22	167
3	MACROSOMIA	18	91
4	BLOOD ZINC DECREASED	15	81
5	HYPOGLYCAEMIC ENCEPHALOPATHY	38	104
6	HYPOGLYCAEMIA	12	71

TOLAZAMIDE (N=100)

	PT_TERM	NONE SUL	TOLAZAMIDE
1	AMBLYOPIA	1	52

Summary

- Sulfonylurea drugs that are target-based had fewer AEs as compared to other diabetes drugs – with the exception of GLICLAZIDE

- Drugs in the sulfonylurea class seem to have better safety profile than other diabetes drugs – *Needs to be validated*

Current Work Includes…

- ***Use metrics other than PRR:***
  - *Modified PRR that accounts for small counts*
  - *Likelihood ratio test-based methods*
- ***Include machine learning approaches and Deep Learning Algorithms to:***
  - *Identify AEs of high significance clinically and statistically*
  - *Provide predictions of AEs for new products*
- ***These are some of the analyses and methods that we are currently incorporating into GSRS system***
- ***openFDA***

Thank You!