Evaluation of Potential Drug-Drug Interactions Among Medications Prescribed in Primary Healthcare Centers for Type 2 Diabetes Mellitus Patients; A Cross-Sectional Study from Palestine.

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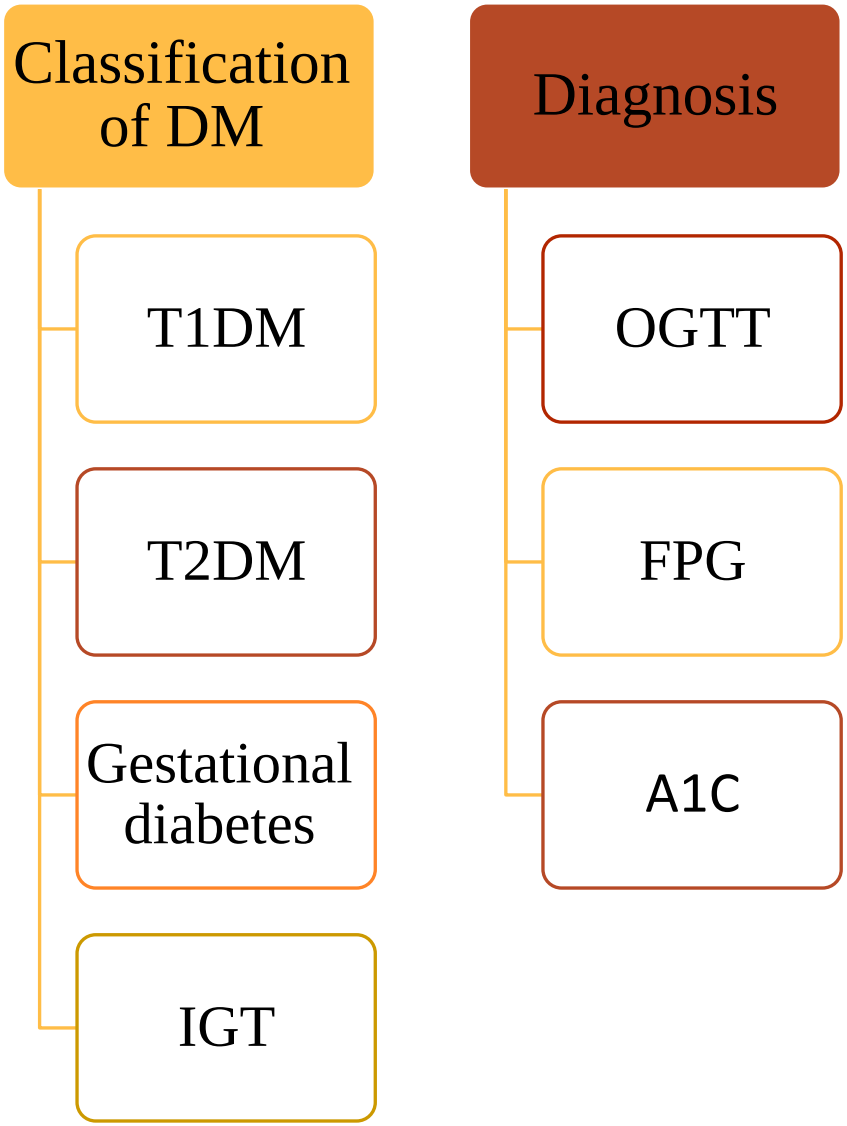
Outline

- Background
- Objectives
- Methods
- Results and Discussion
- Conclusions

Background

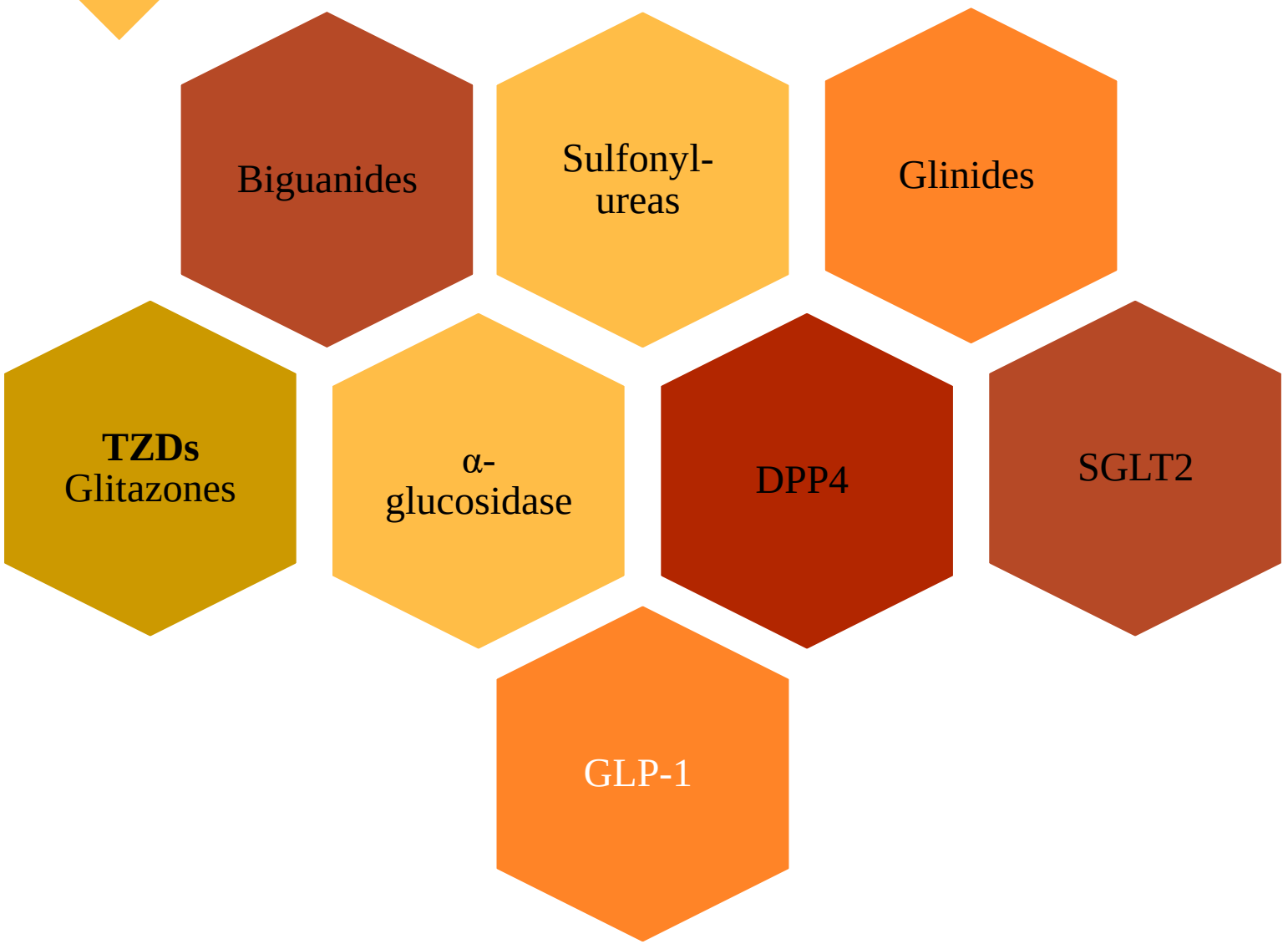
1. **Pharmacokinetics interaction (ADME).**
2. **Pharmacodynamic interactions**
3. **Prevalence of DDIs.**
4. **Diabetes mellitus definition and prevalence**

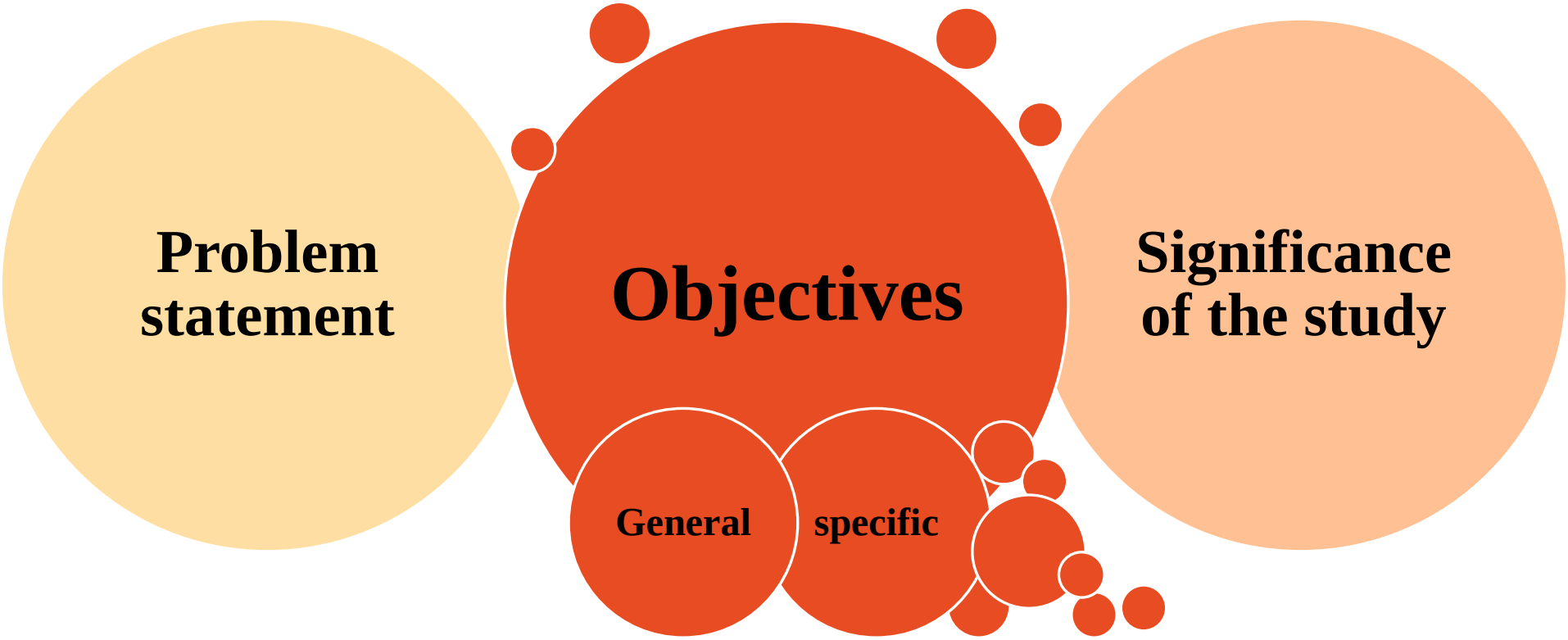
Diabetes mellitus

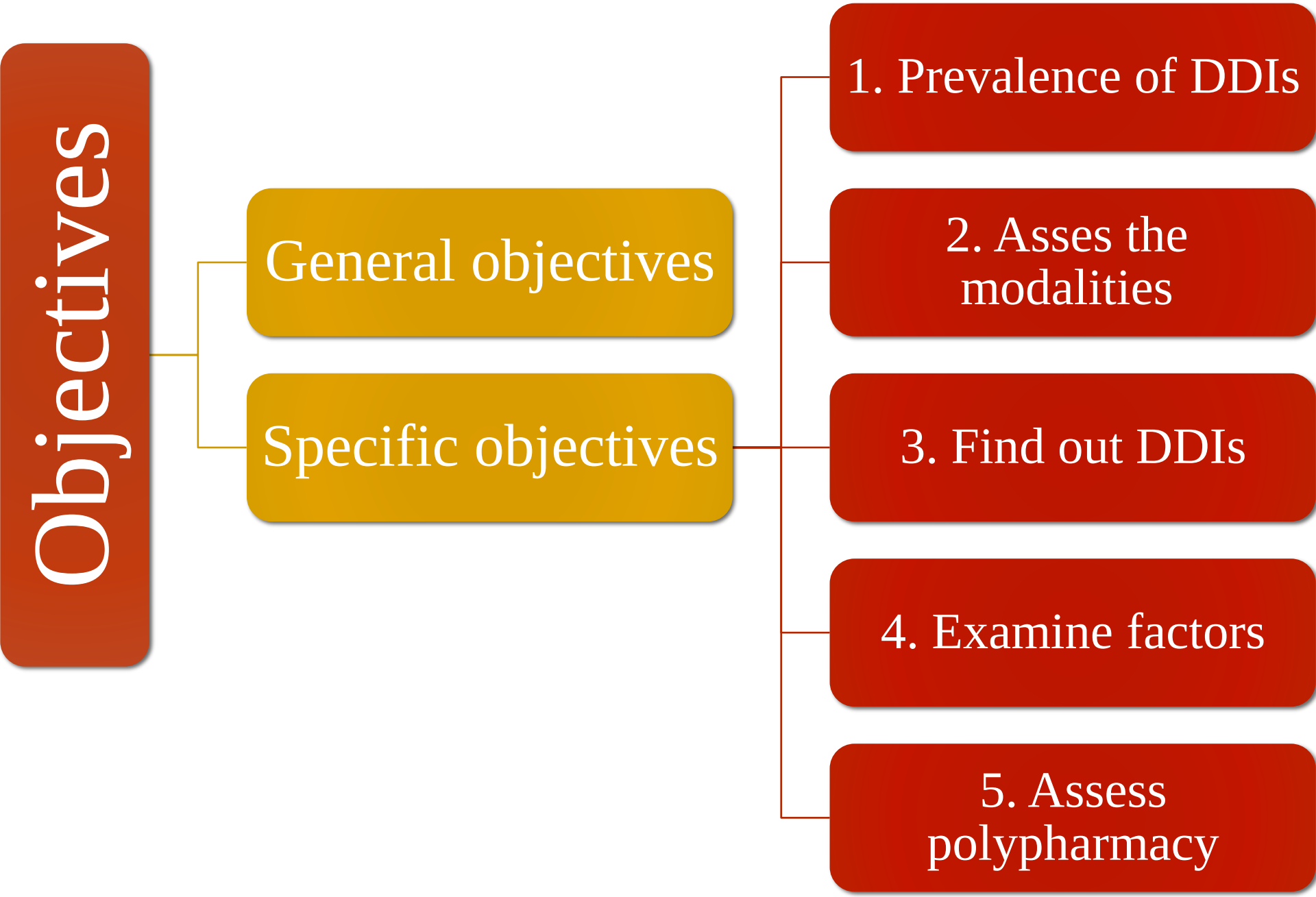


DM

• Treatment of DM




Problem statement
Objectives
General
specific
Significance of the study


Objectives
General objectives
Specific objectives
1. Prevalence of DDIs
2. Asses the modalities
3. Find out DDIs
4. Examine factors
5. Assess polypharmacy

Methodology

Study design

Observational retrospective design

Study setting

Primary health care centers of MOH, Southern part of west bank

Pop. & selection criteria

All T2DM whom visited primary health care centers

Sample size

400 diabetic patients

Data collection

Questionnaire
Lexicomp checker
Risk rating classification

Ethical consideration

IRB , MOH
Informed verbal consent

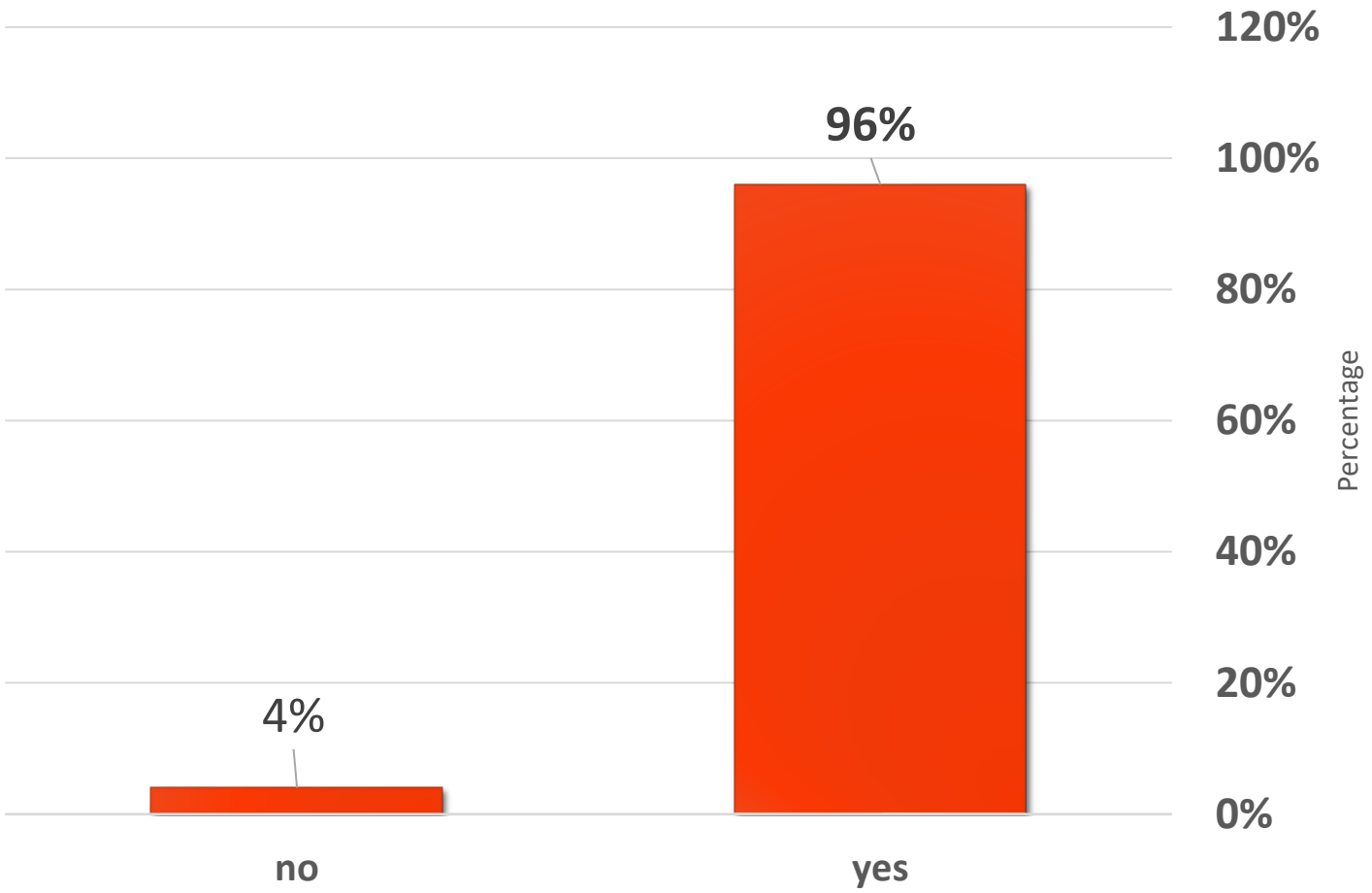
Statistical analysis

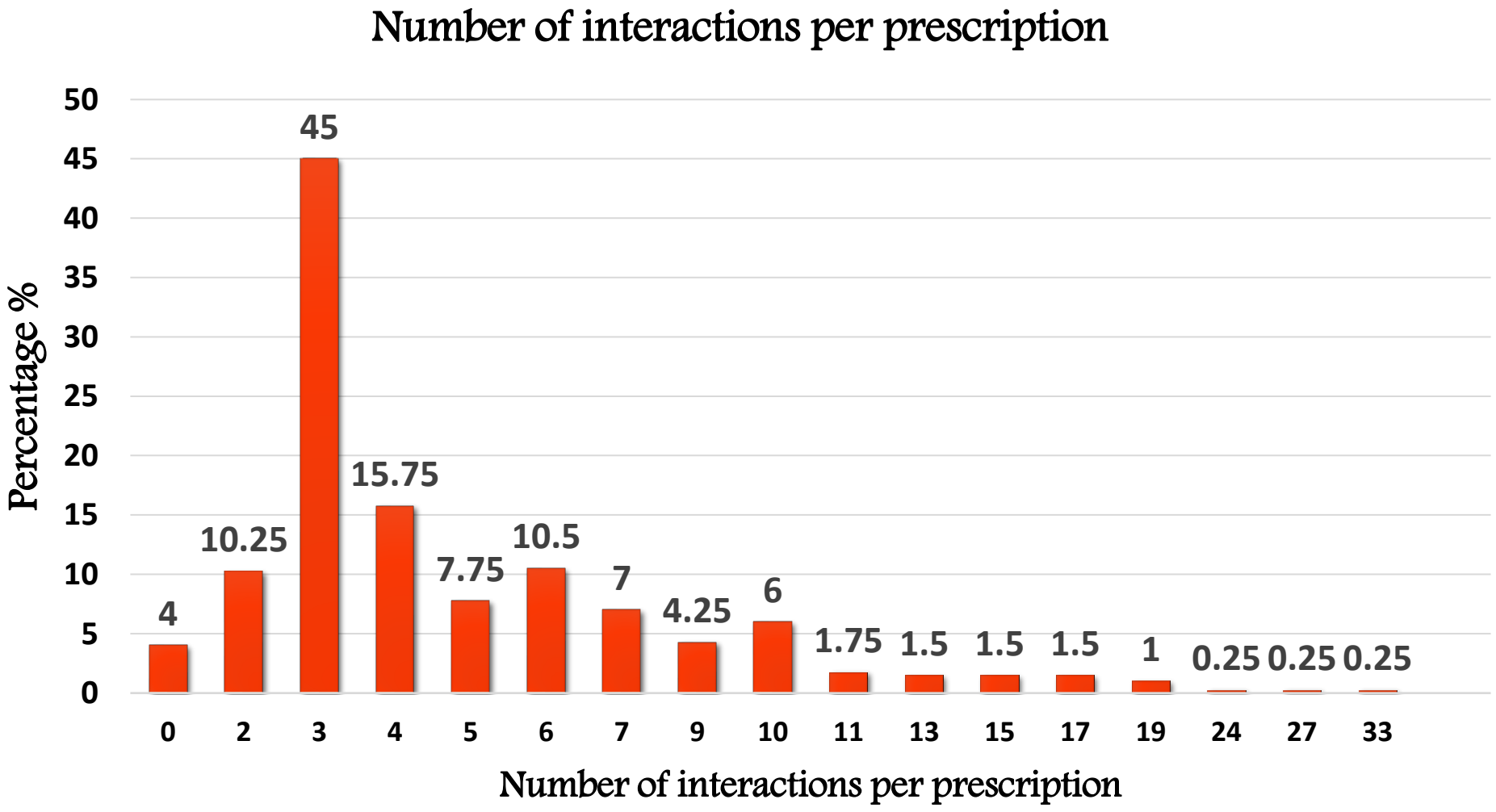
SPSS
Man-Whitney-U & Kruskal-Wallis test
P-values < 0.05

Results and discussion

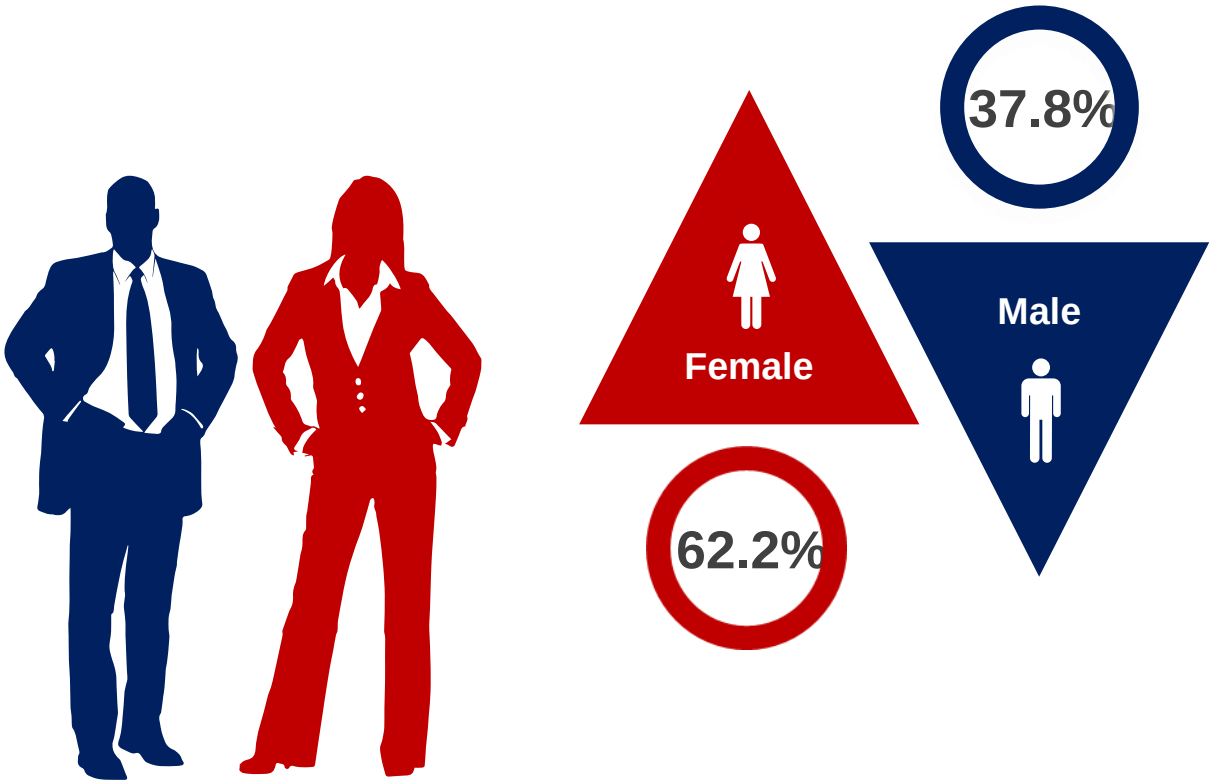
- Socio-demographic characteristics of participating patients
- Prescribing pattern of medications in DM patients
- Co-morbid conditions
- Evaluation of potential DDIs
- Factors associated with potential DDIs

Prevalence of DDIs

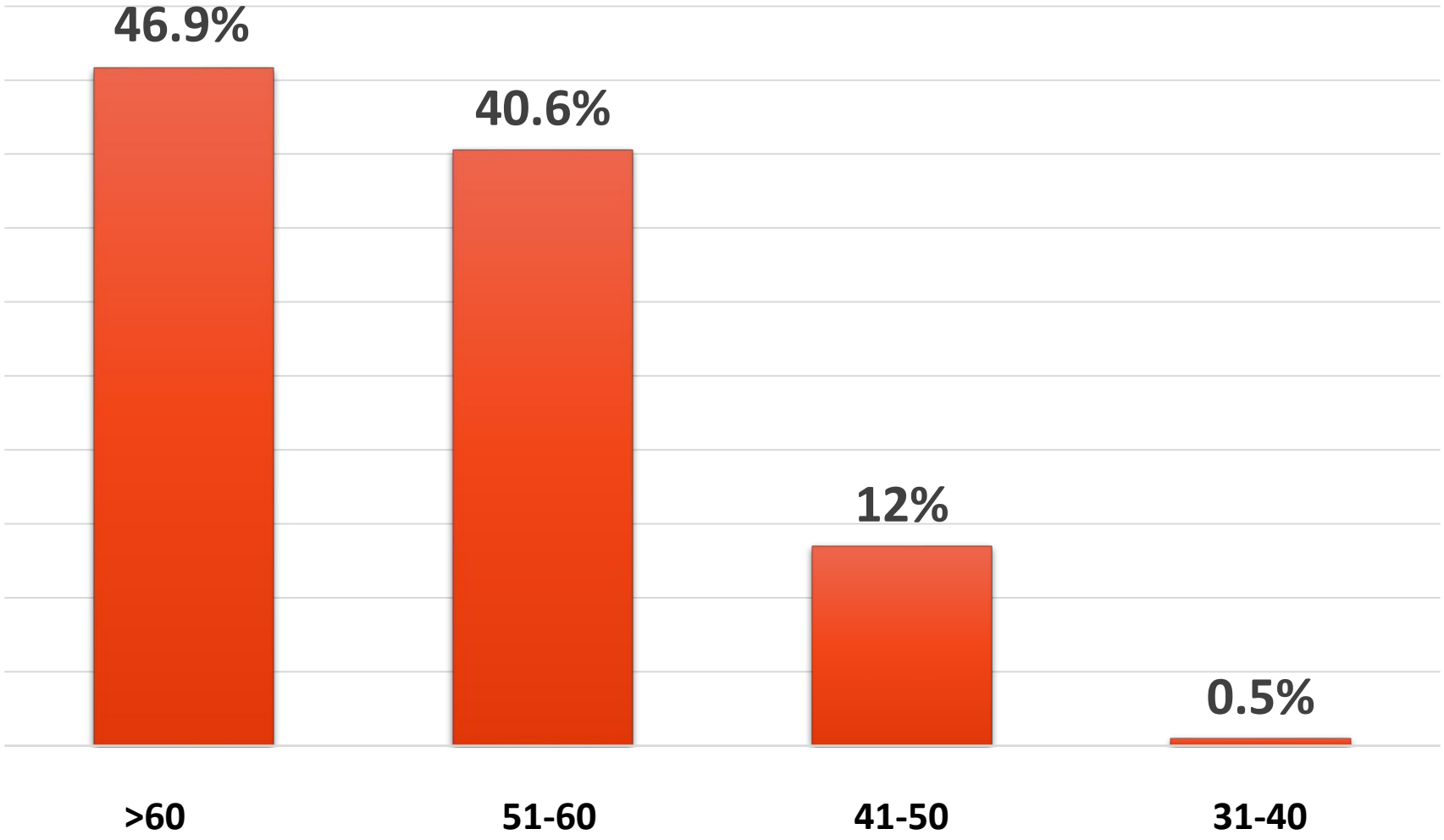



Number of interactions per prescription
Percentage %
50
45
40
35
30
25
20
15
10
5
0
4
10.25
45
15.75
7.75
10.5
7
4.25
6
1.75
1.5
1.5
1.5
1
0.25
0.25
0.25
0
2
3
4
5
6
7
9
10
11
13
15
17
19
24
27
33
Number of interactions per prescription

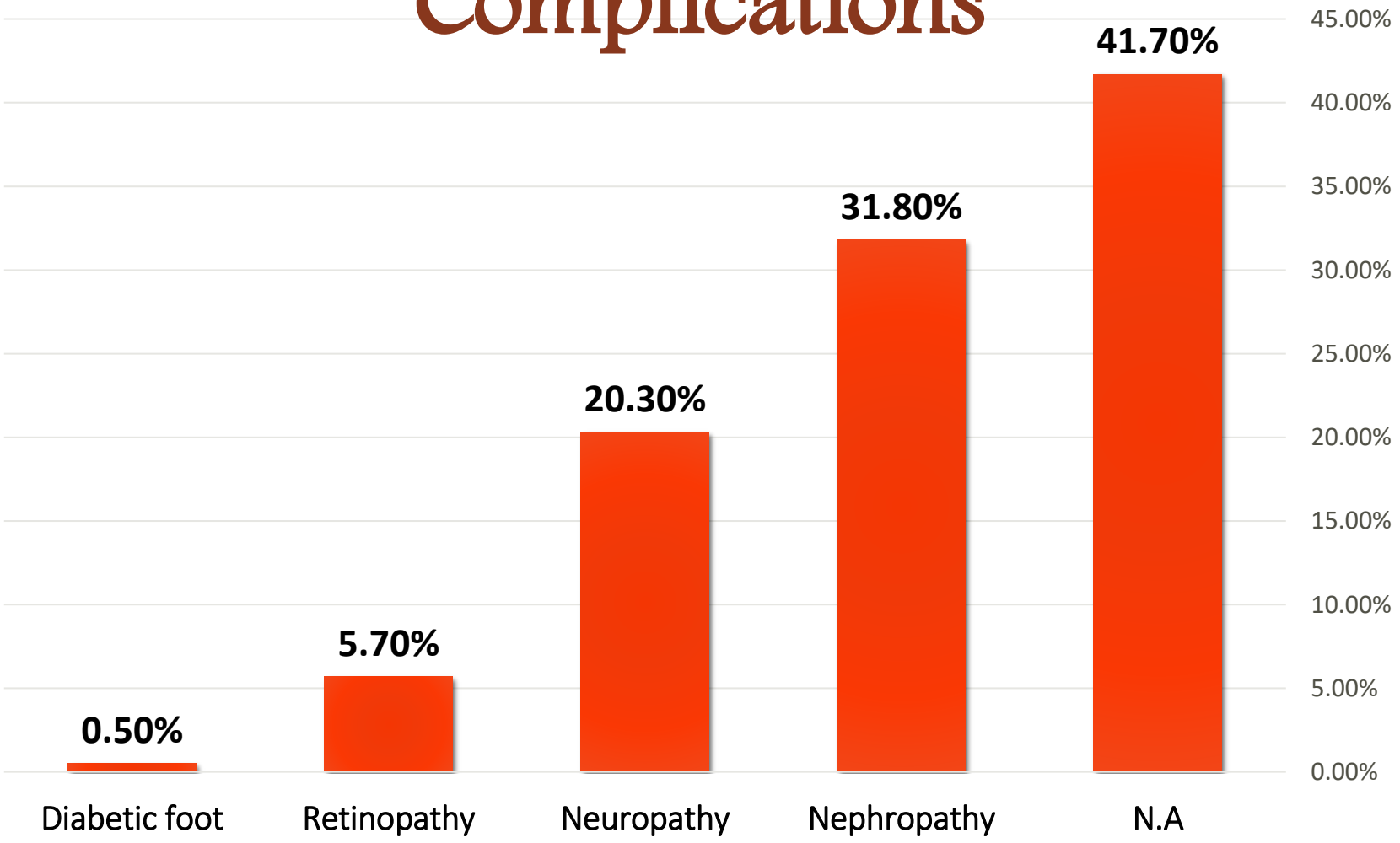
Gender



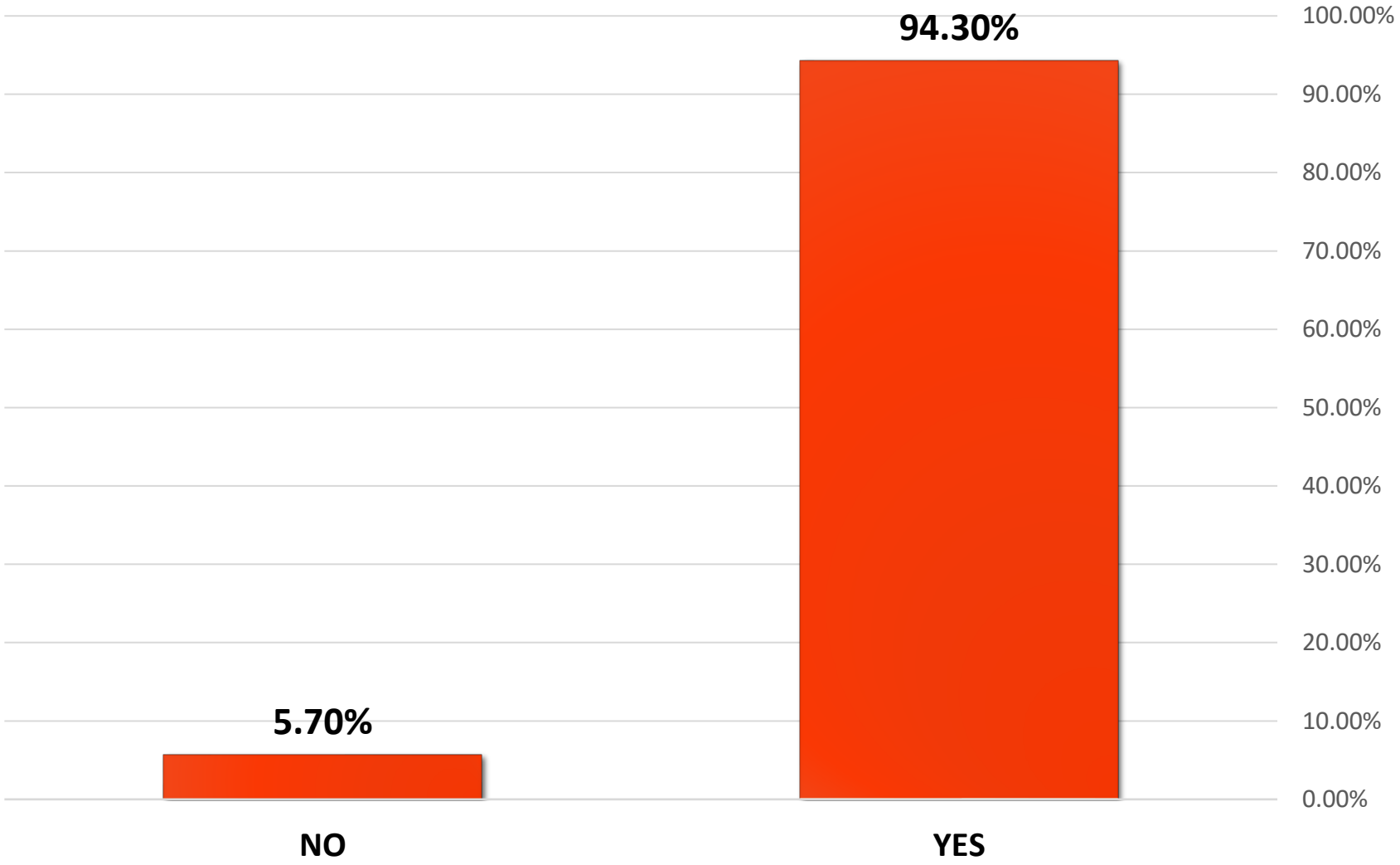
Age Category



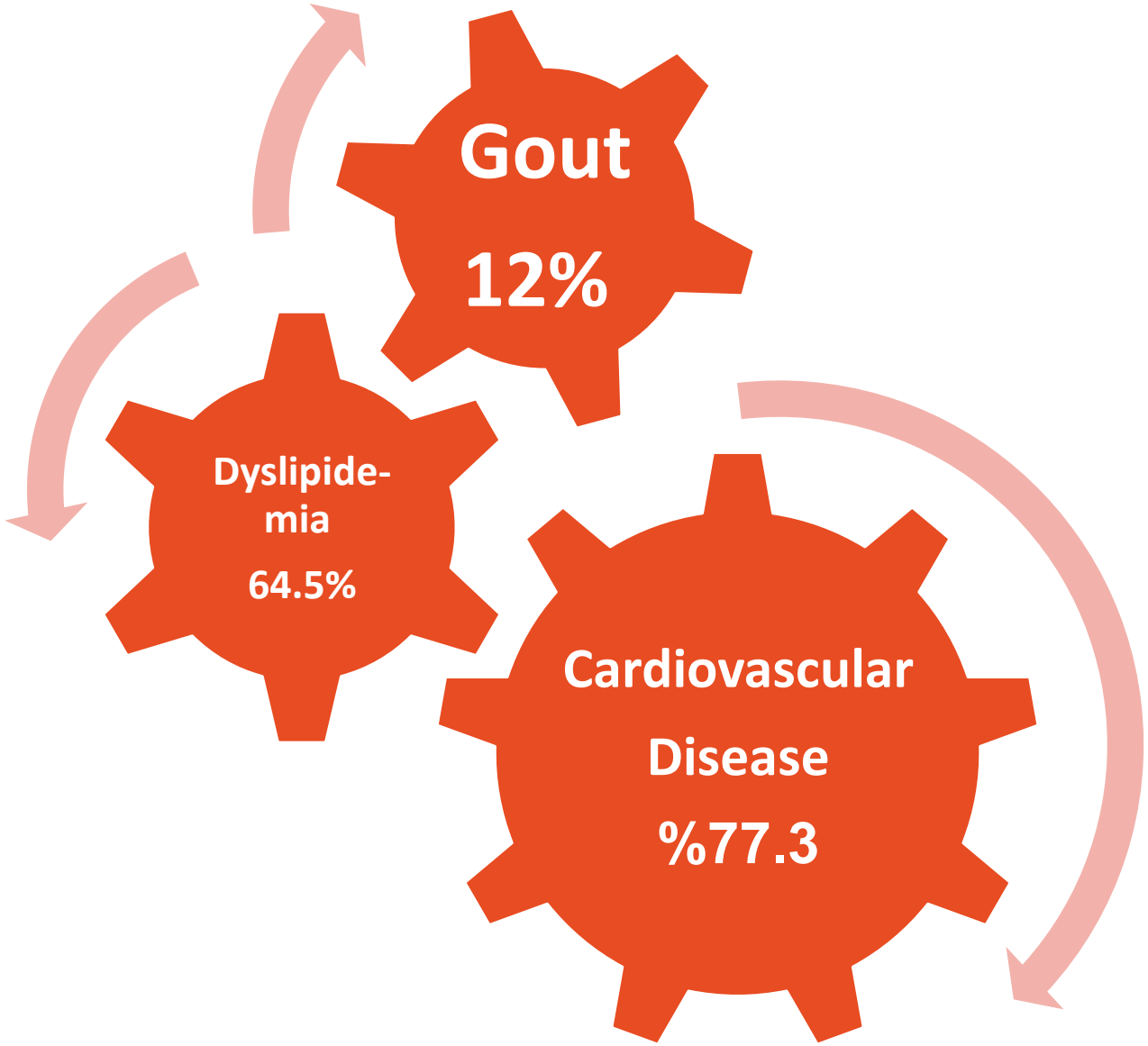
Complications



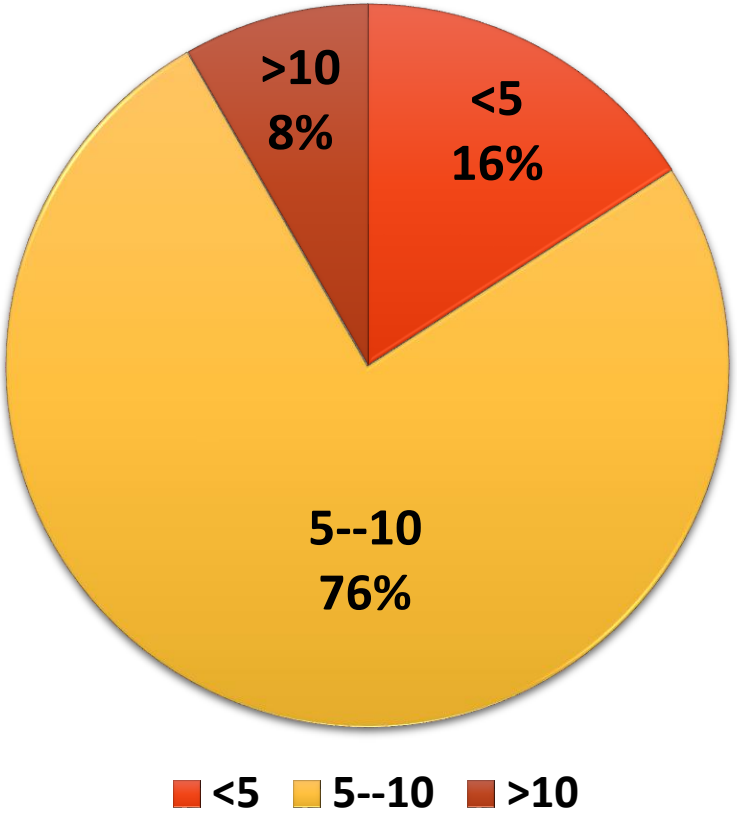
Comorbidities



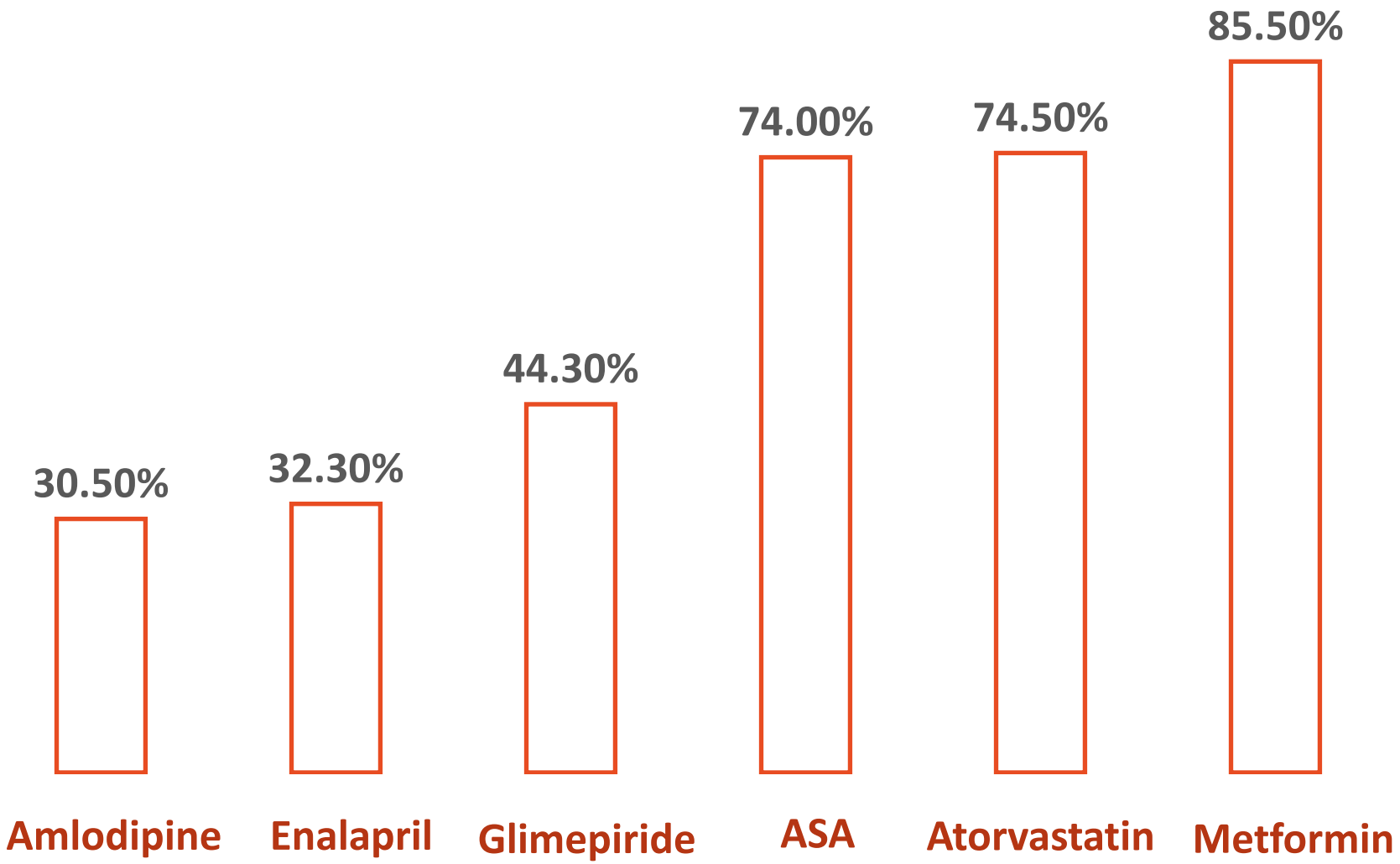
Comorbidities among DM patients



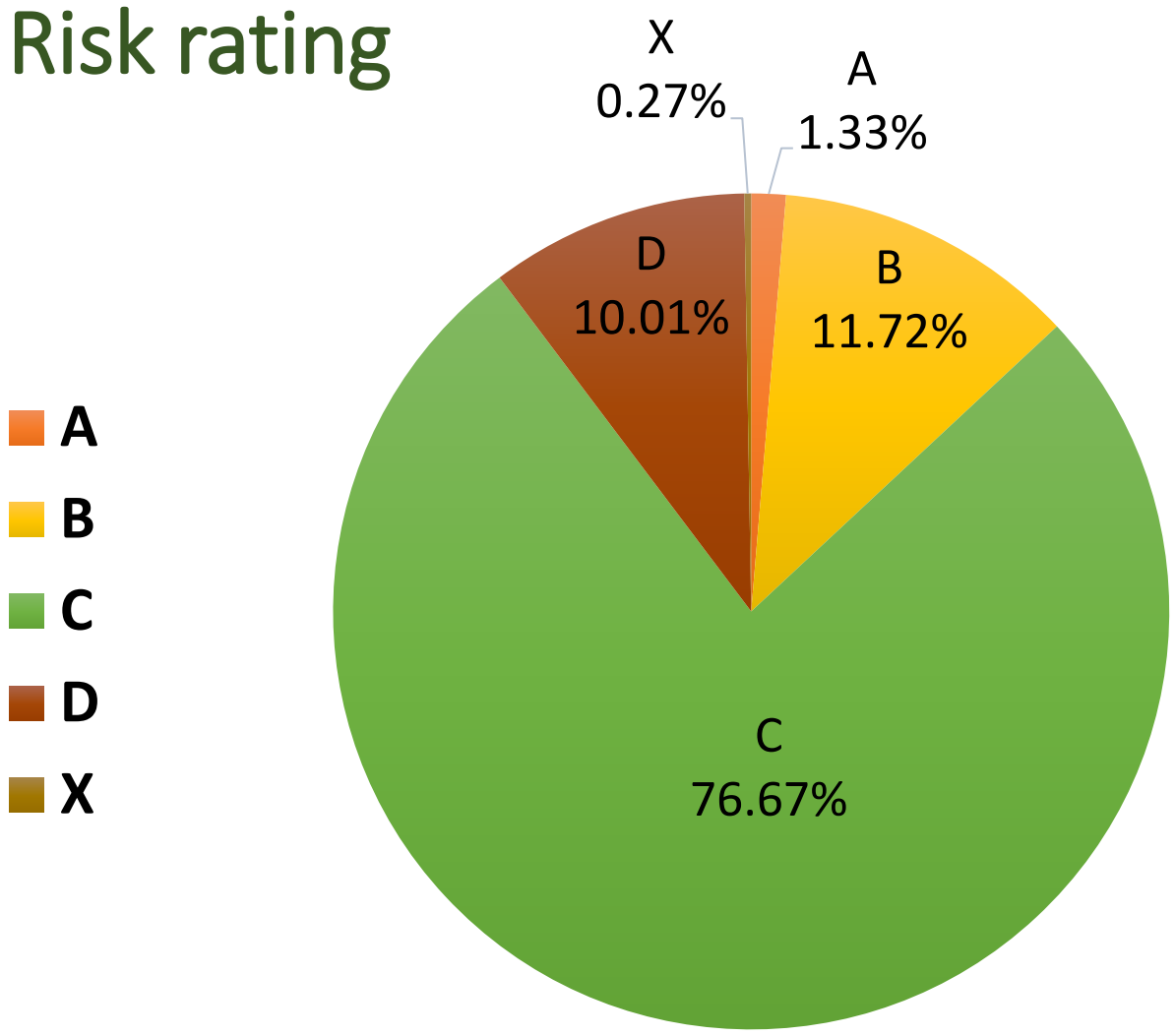
PolyPharmacy



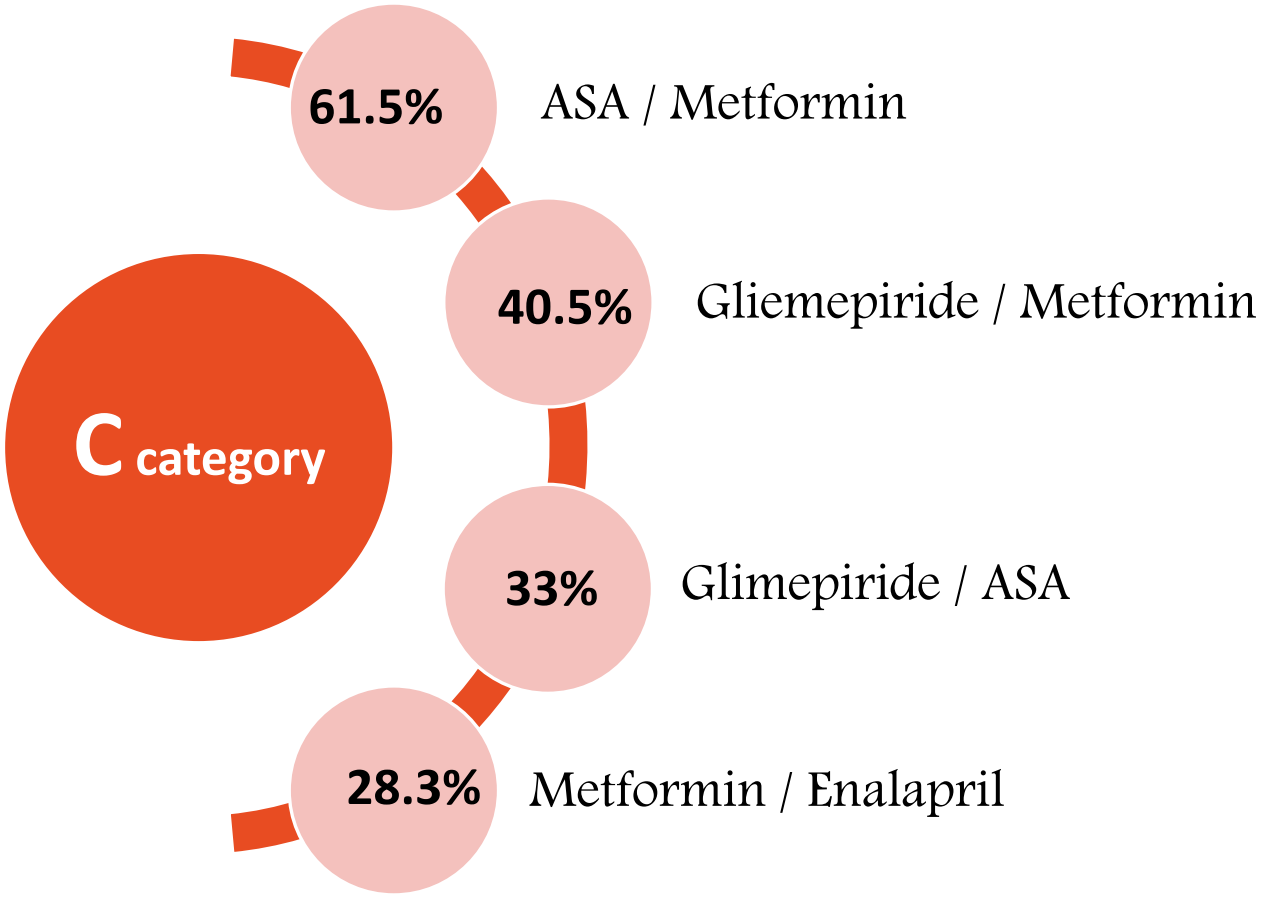
Top prescribed medications



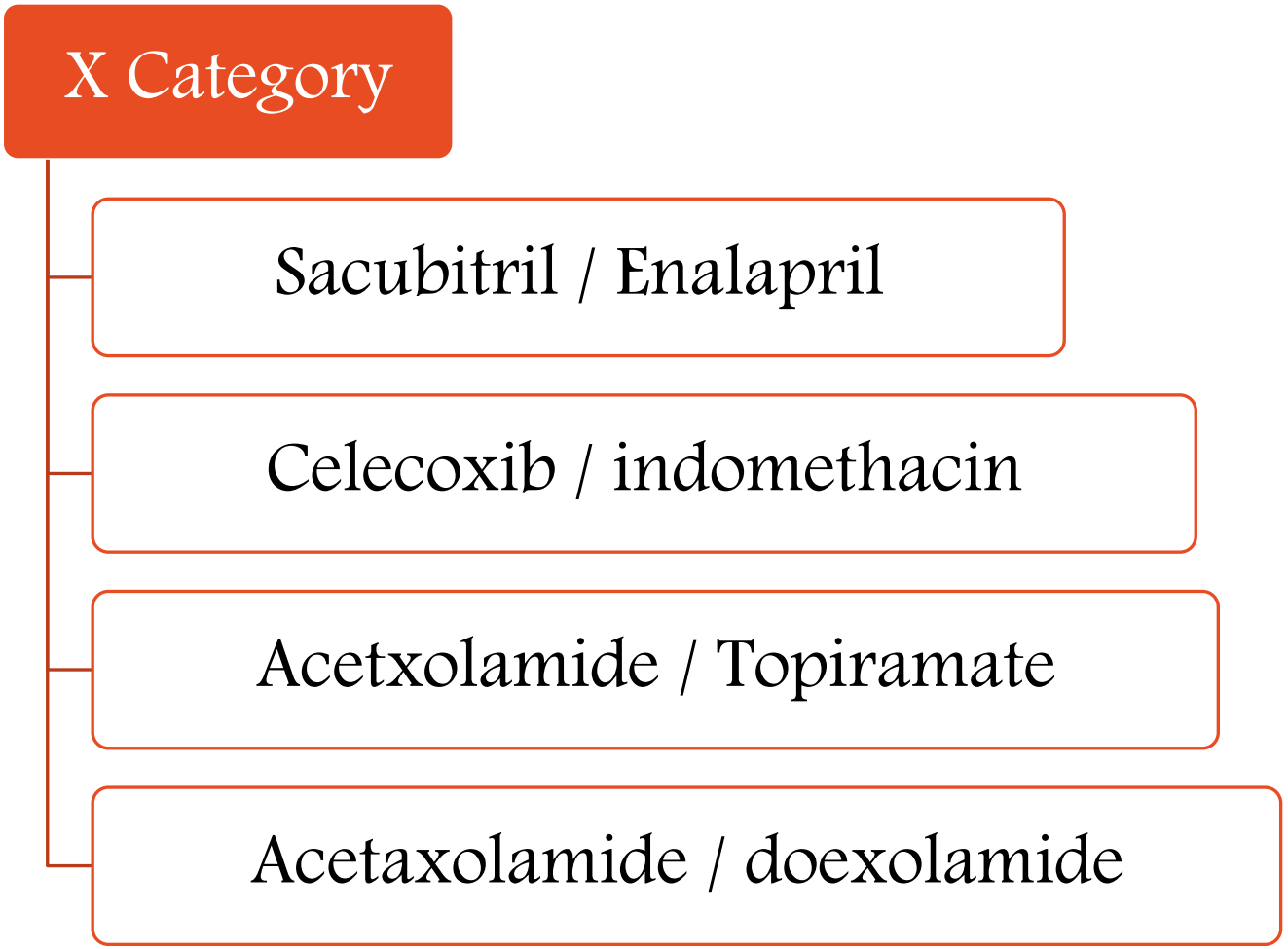
Risk rating



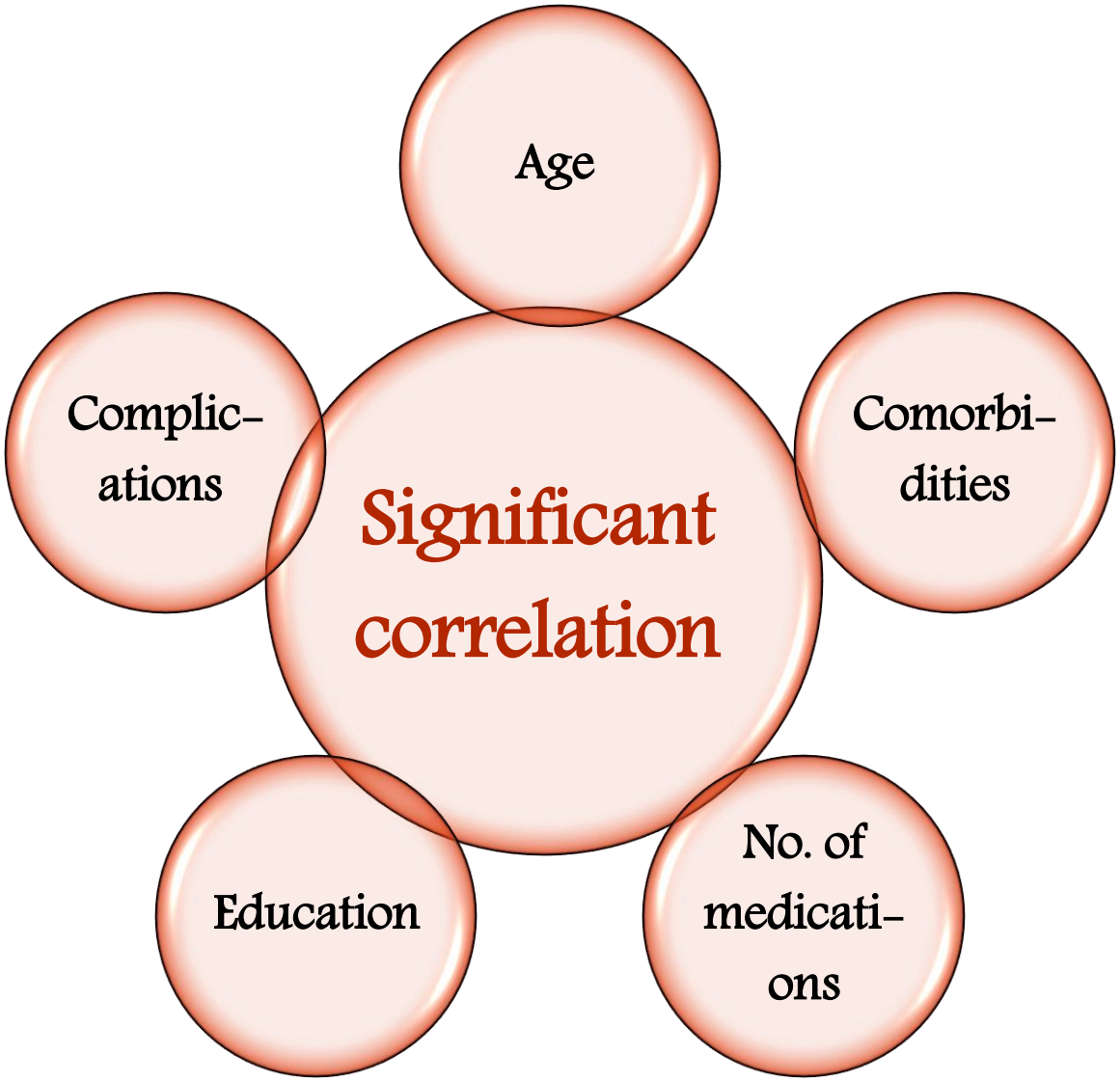
Top four drug pairs with MODERATE risk rating

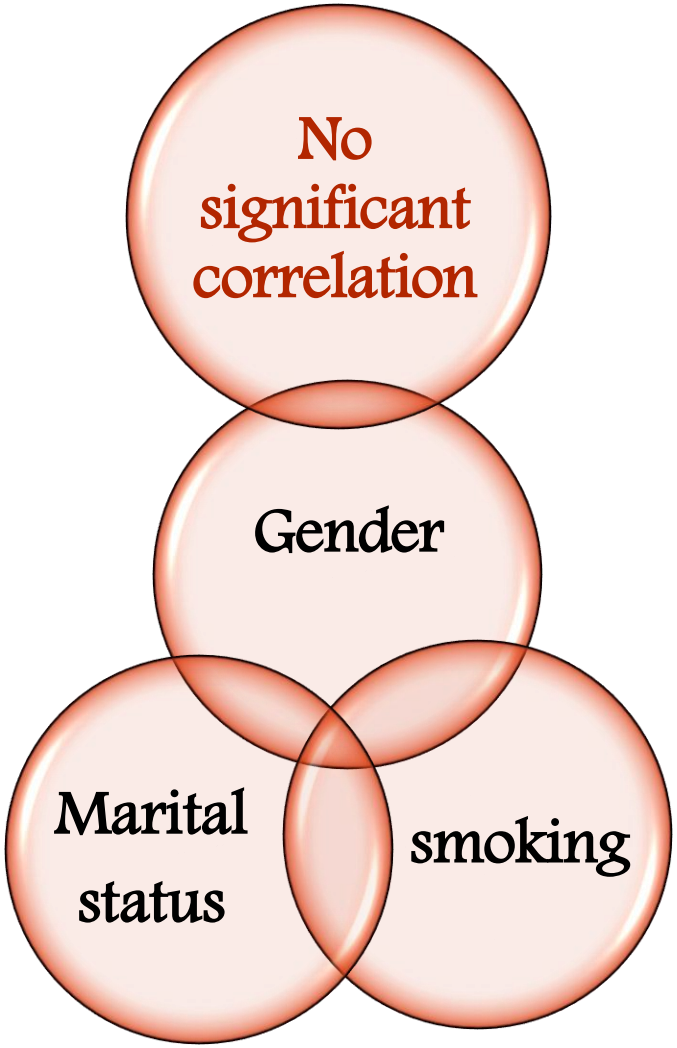


Drug pairs with MAJOR risk rating



Factors associated with potential DDIs





Conclusions

The prevalence of potential DDIs among T2DM is very common

Health, social and economic consequences associated with PP.

Be more ware, monitoring potential interaction while prescribing.

Recommendations

Moderate DDIs should be monitoring.

Potentially class D,X DDIs should be avoided, and generalize major DDIs to health care centers.

Suspected adverse drug interactions should be reported

Include a clinical pharmacist among health care providers

Updated database system to check DDIs

Risk class	Action	Description
A	No known interaction	Data has not demonstrated either pharmacodynamic or pharmacokinetic interactions between the specified agents.
B	No action needed	Data demonstrates that the specified agents may interact with each other, but there is little to no evidence of clinical concern resulting from their concomitant use.
C	Monitor therapy	Data demonstrates that the specified agents may interact with each other in a clinically significant manner. The benefits of concomitant use of these two medications usually outweigh the risks. An appropriate monitoring plan should be implemented to identify potential negative effects. Dosage adjustments of one or both agents may be needed in a minority of patients.
D	Consider therapy modification	Data demonstrate that the two medications may interact with each other in a clinically significant manner. A patient- specific assessment must be conducted to determine whether the benefits of concomitant therapy outweigh the risks. Specific actions must be taken in order to obtain the benefits and/or minimize the toxicity resulting from concomitant use of the agents. These actions may include aggressive monitoring, empiric dosage changes, and choosing alternative agents.
X	Avoid combination	Data demonstrates that the specified agents may interact with each other in a clinically significant manner. The risks associated with concomitant use of these agents usually outweighs the benefits. These agents are generally considered contraindicated.

Limitations

- Sampling method was simple
- Patient integrity of reporting information
- Generalization of the results is limited

Socio-demographic characteristics of participating patients

Characteristics	Frequency	percentage
Age category		
31-40	2	0.5%
41-50	54	13.5%
51-60	161	40.3%
>60	183	45.8%
Patient's gender		
Male	152	38.0 %
Female	248	62.0 %
Marital status		
Single	4	1.0 %
Married	357	89.3 %
Widowed	37	9.3 %
Divorced	2	0.5 %
Living place		
City	153	38.3 %
Village	247	61.8 %
Educational level		
Primary	185	46.3 %
High school	65	16.3 %
University	47	11.8 %
None	103	25.8 %
Employment status		
Yes	96	24.0 %
No	304	76.0 %
Smoking		
Smoker	53	13.3 %
Nonsmoker	347	86.8 %
Monthly income (NIS)		
≥ 2500	110	27.5 %
< 2500	290	72.5 %

Top 20 prescribed medications used by patients included in the study

No.	Medication	Frequency	Percentage (%)
1.	Metformin	342	85.5 %
2.	Atorvastatin	298	74.5 %
3.	ASA	296	74.0 %
4.	Glimepiride	177	44.3 %
5.	Enalapril	129	32.3 %
6.	Amlodipine	122	30.5 %
7.	Ranitidine	112	28.0 %
8.	Bisoprolol	107	26.8 %
9.	Furosemide	106	26.5 %
10.	Carbamazepine	83	20.8 %
11.	Alfacalcidol	80	20.0 %
12.	Calcium	53	13.3 %
13.	Losartan	47	11.8 %
14.	Allopurinol	44	11.0 %
15.	Clopidogrel	43	10.8 %
16.	Hydrochlorothiazide	35	8.8 %
17.	Omeprazole	35	8.8 %
18.	Atenolol	32	8.0 %
19.	Spironolactone	23	5.8 %
20.	Valsartan	21	5.3 %

Comorbidities among DM patients

No.	Disease	Frequency	Percentage (%)
1.	Cardiovascular disease	309	77.3 %
2.	Dyslipidemia	258	64.5 %
3.	Gout	48	12.0 %
4.	Infectious disease	38	9.5 %
5.	Thyroid	22	5.5 %
6.	Asthma	14	3.5 %
7.	BPH	12	3.0 %
8.	GI Upset	10	2.5 %
9.	Allergy	10	2.5 %
10.	Neurologic disorders	7	1.8 %
11.	Cancer	3	0.8 %
12.	Surgery	2	0.5 %
13.	Renal disease	1	0.3 %
14.	Contraceptive	1	0.3 %

Top 20 potential drug-drug interactions

No.	Drug-drug interactions	Frequency, %	Risk rating	Severity	Cause and effect
1.	ASA/Metformin	246 (61.5)	C	Moderate	Salicylates may enhance the hypoglycemic effect of blood glucose lowering agents.
2.	Glimepiride/Metformin	162 (40.5)	C	Moderate	Antidiabetic agents may enhance the hypoglycemic effect of hypoglycemia-associated agents.
3.	Glimepiride/ASA	132, (33.0)	C	Moderate	Salicylates may enhance the hypoglycemic effect of blood glucose lowering agents.
4.	Metformin/Enalapril	113, (28.3)	C	Moderate	ACE inhibitors may enhance the adverse / toxic effect of metformin. This includes both a risk for hypoglycemia and for lactic acidosis.
5.	Enalapril/ASA	97, (24.3)	C	Moderate	Salicylates may enhance the nephrotoxic effect of ACE inhibitors. Salicylates may diminish the therapeutic effect of ACE inhibitors.
6.	Insulin/Metformin	82, (20.5)	C	Moderate	Antidiabetic agents may enhance the hypoglycemic effect of hypoglycemia associated agents.
7.	ASA/Furosemide	82, (20.5)	C	Moderate	Salicylates may diminish the diuretic effect of Loop Diuretics. Loop Diuretics may increase the serum concentration of Salicylates.
8.	Metformin/Furosemide	77, (19.3)	C	Moderate	Hyperglycemia associated agents may diminish the therapeutic effect of antidiabetic agents.
9.	Atorvastatin/Carbamazepine	63, (15.8)	D	Slightly severe	Carbamazepine (CYP3A4 Inducers / strong) may increase the metabolism of Atorvastatin (CYP3A4 Substrates).
10.	Glimepiride/Enalapril	58, (14.5)	B	Minor	ACE inhibitors may enhance the hypoglycemic effect of blood glucose lowering agents
11.	Insulin/Enalapril	53, (13.3)	B	Minor	ACE inhibitors may enhance the hypoglycemic effect of blood glucose lowering agents
12.	Insulin/Furosemide	49, (12.3)	C	Moderate	Hyperglycemia-Associated agents may diminish the therapeutic effect of antidiabetic agents.
13.	Alfacalcidol/Calcium	46, (11.5)	C	Moderate	Calcium salts may enhance the adverse / toxic effect of Vitamin D analogs.
14.	Glimepiride/Ranitidine	41, (10.3)	C	Moderate	Ranitidine may increase the serum concentration of Sulfonylureas.
15.	ASA/Calcium	41, (10.3)	B	Minor	Antacids may decrease the serum concentration of salicylates.
16.	Clopidogrel/Atorvastatin	39, (9.8)	B	Minor	Atorvastatin may diminish the antiplatelet effect of clopidogrel.
17.	ASA/Clopidogrel	37, (9.3)	C	Moderate	Agents with antiplatelet properties may enhance the adverse / toxic effect of salicylates. Increased risk of bleeding may result.
18.	Insulin/Bisoprolol	36, (9.0)	C	Moderate	Beta blockers may enhance the hypoglycemic effect of insulins.
19.	Enalapril/Furosemide	35, (8.8)	C	Moderate	Loop diuretics may enhance the hypotensive effect of ACE inhibitors. Loop diuretics may enhance the nephrotoxic effect of ACE inhibitors.
20.	Glimepiride/Furosemide	35, (8.8)	C	Moderate	Hyperglycemia-Associated Agents may diminish the therapeutic effect of Antidiabetic Agents.

Top five drug pairs with major risk rating (x category)

NO.	Drug-drug interactions	Frequency	Percentage	Risk rating
1.	Atorvastatin/Carbamazepine	63	15.8%	D
2.	Amlodipine/Carbamazepine	23	5.8%	D
3.	Bisoprolol/Carbamazepine	20	5.0%	D
4.	Losartan/Carbamazepine	12	3.0%	D
5.	ASA/Indomethacin	6	1.5%	D
6.	Isosorbide dinitrate/Carbamazepine	5	1.3%	D
7.	Levothyroxine/Calcium	5	1.3%	D
8.	Glimepiride/Vildagliptin	5	1.3%	D
9.	Insulin/Vildagliptin	4	1.0%	D
10.	ASA/Diclofenac	3	0.8%	D
11.	Enalapril/Losartan	3	0.8%	D
12.	Enalapril/Candesartan	3	0.8%	D
13.	Clopidogrel/Omeprazole	3	0.8%	D
14.	Furosemide/Diclofenac	2	0.5%	D
15.	Acetazolamide/ASA	2	0.5%	D
16.	ASA/Ibuprofen	2	0.5%	D
17.	Budesonide/Calcium	1	0.3%	D
18.	Clopidogrel/Pantoprazole	1	0.3%	D
19.	Clopidogrel/Esomeprazole	1	0.3%	D
20.	Sacubitril/Enalapril	1	0.3%	X
21.	Celecoxib/Indomethacin	1	0.3%	X
22.	Furosemide/Celecoxib	1	0.3%	D
23.	Levofloxacin/Calcium	1	0.3%	D
24.	Amlodipine/Erythromycin	1	0.3%	D
25.	Topiramate/ASA	1	0.3%	D
26.	Topiramate/Carbamazepine	1	0.3%	D
27.	Acetazolamide/Topiramate	1	0.3%	X
28.	Acetazolamide/Dorzolamide	1	0.3%	X
29.	Glimepiride/Fluconazole	1	0.3%	D
30.	Etoricoxib/Indomethacin	1	0.3%	X
31.	Etoricoxib/ASA	1	0.3%	D
32.	Etoricoxib/Carbamazepine	1	0.3%	D
33.	Insulin/Dapagliflozin	1	0.3%	D
34.	Clopidogrel/Lansoprazole	1	0.3%	D
35.	Carbamazepine/Theophyline	1	0.3%	D
36.	Furosemide/Indomethacin	1	0.3%	D
37.	Glimepiride/Indomethacin	1	0.3%	D

Univariate analysis of factors associated with potential DDIs.

Characteristic	Frequency % N = 400	Number of DDIs Median (Q1 – Q3)	p-value
Gender			
Male	152 (38 %)	5 (3 - 8.75)	0.404
Female	248 (62 %)	6 (3 - 9)	
Age category			
31-40	2 (0.5 %)	2.5 (2 - 3)	0.000
41-50	54 (13.5 %)	3 (1 -6)	
51-60	161 (40.25 %)	5 (3 - 8)	
>60	183 (45.75 %)	6 (3 - 10)	
Marital status			
Single	4 (1 %)	6 (4 -11.5)	0.088
Married	357 (89.25 %)	5 (3 -9)	
widowed	37 (9.25 %)	7 (3 -14)	
Divorced	2 (0.5 %)	2 (1 -3)	
Educational level			
Primary	185 (46.25 %)	6 (3 - 9)	0.000
High school	65 (16.25 %)	4 (1 - 8)	
bachelor	47 (11.75 %)	4 (1 - 6)	
none	103 (25.75 %)	6 (3 - 10)	
Smoking			
Smoker	347 (86.75 %)	5 (2.5 - 8)	0.279
Non smoker	53 (13.25 %)	5 (3 -9)	
Others drug?			
Yes	374 (93.5 %)	6 (3 - 9)	0.000
No	26 (6.5 %)	1 (1 - 3)	
Number of medications			
<5	76 (19 %)	1 (1 - 3)	0.000
5 – 10	292 (73 %)	6 (4 - 9)	
>10	32 (8 %)	16.5 (13.25 - 20)	