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Original Research Article

Factors Associated with Treatment Response to Antidiabetic Agents in Compliant Type 2 Diabetes Mellitus Patients: A Brief Summary of 5-Year Data

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Abstract

Purpose: *To evaluate the response to diabetic medications and factors influencing drug response in compliant type 2 diabetes mellitus (T2DM) patients.*
Methods: *A cross-sectional, retrospective study was performed on 100 T2DM patients at the University Malaya Medical Centre (UMMC) who were prescribed with at least one antidiabetic medication between January 2007 and December 2011.*
Results: *Using data from their medical records, it was determined that both fasting plasma glucose (FPG) and glycated hemoglobin (A1c) levels among all subjects were lower than baseline values. However, the reductions were not significant ($p = 0.239$ and $p = 0.093$). Factors that were significantly associated with the response to diabetic medications, include hypertension ($p = 0.011$), sulfonylureas ($p = 0.041$), beta-blockers ($p = 0.005$), and baseline A1c levels ($p < 0.001$).*
Conclusion: *Treatment of T2DM can be further optimized to ensure that diabetes is well-controlled.*

Keywords: *Treatment response; Antidiabetics; Type 2 Diabetes Mellitus, Hypertension, Beta-blocker.*

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INTRODUCTION

Management of T2DM can be achieved in two ways, namely, lifestyle modification and pharmacotherapy. In Malaysia, pharmacotherapy is usually initiated when lifestyle modification fails to achieve glycemic targets (i.e., A1c < 6.5 % and FPG < 6 mmol/L) within 3 months [1].

Pharmacotherapy of T2DM involves the use of antidiabetic medications to reduce glycated hemoglobin (A1c) and fasting plasma glucose (FPG) levels to the targeted range. The antidiabetic medications available in Malaysia include insulin, oral hypoglycemic agents (OHAs), and GLP-1 analogue (exenatide) [1]. In the latest Malaysian clinical practice guidelines, metformin was recommended as the first-line agent for the treatment of T2DM [1]. Other OHAs, such as sulfonylureas and thiazolidinediones, can also be used as first-line therapy. OHAs can be used in combination with insulin, exenatide, or other OHAs, if glycemic control is not achieved with monotherapy [1].

According to the Malaysian Statistics on Medicine 2007 [2], metformin, glibenclamide, and gliclazide are among the top 10 drugs used in Malaysia. In the same report, the cost burden of antidiabetic medications was also the second highest in 2007, which was > Ringgit Malaysia (RM) 195 million [2]. Therefore, it is important to

ensure that the optimum antidiabetic regimen is employed to achieve glycemic control without incurring unnecessary costs.

While foreign data are widely available on the comparative effectiveness of medications for T2DM, local data for Malaysia, data concerning the therapeutic effectiveness of antidiabetic medications are very limited. There is also lack of existing information regarding how the various factors influencing drug response are applied in clinical setting.

Given that antidiabetic drugs are the most utilized drug group in Malaysia, the present study aims to evaluate the response of compliant T2DM patients to diabetes medications, as well as the factors influencing the drug response.

METHODS

Study population and time frame

Subjects were patients > 18 years of age who have been diagnosed with T2DM, according to the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) code for T2DM (E11.0-E11.9). Subjects were also currently or previously prescribed at least one antidiabetic medication during this study, either as a monotherapy or a combination therapy. This study was conducted between January 2007 and December 2011 at the University Malaya Medical Centre Kuala Lumpur, Malaysia.

Exclusion criteria

Patients diagnosed with Type 1 Diabetes Mellitus (T1DM) or those diagnosed with T2DM, but never received any antidiabetic medications or non-pharmacological management, were excluded from this study. Patients that were found to be non-compliant to antidiabetic medications were also excluded.

Study Design and Procedures

The present study was a cross-sectional, retrospective study that was initiated after receiving approval from the Medical Ethics Committee of University of Malaya Medical Centre (UMMC). This study was in accordance with the Declaration of Helsinki[3].

Patients that fulfilled the requirements of the ICD-10 code for T2DM (E11.0-E11.9) were identified using the Hospital Information System (HIS). Subsequently, the medical records were traced and retrieved from the Patient Medical Records (PMR) office using registration numbers. If the patient's record met all the inclusion criteria, data collection was performed. A total of 100 eligible subjects were identified via convenient sampling and their records were retrieved for this study. A minimum sample size of 93 patients was determined to be necessary for statistical purposes using Epi Info, version 6 (Centers for Disease Control and Prevention, Atlanta, GA).

Demographic information and clinical characteristics, including age, gender, ethnicity, height, weight, duration of diabetes, comorbidities, history of taking antidiabetic drugs, other concurrent medications, FPG, A1c, and other laboratory results, of each patient were extracted using the Data Collection Form.

A "treatment response" was defined as an achievement of the glycemic targets (i.e., A1c < 6.5 %, FPG < 6 mmol/L) [1]. The minimum period required prior to assessing the response to diabetic medications was 3 months after baseline recording, which was defined as the first recording available for FPG and A1c levels [1].

Data analysis

The baseline and recent levels of FPG and A1c were analyzed qualitatively and quantitatively using Pearson's Chi-squared test and paired samples t-test. The most recent A1c reading was chosen as an indicator of response to the antidiabetic medications. The mean and standard deviation of recent A1c levels were calculated for each patient characteristic and medication. For each of these factors, an independent samples t-test was performed to assess its significance in the response to the antidiabetic medication(s).

All data were pooled and analyzed using IBM SPSS Statistics 20.0 (Armonk, NY, USA). Categorical results were presented in the form of frequency tables and graphs. Numerical results were expressed as mean ± standard deviation (SD). Comparisons between groups were conducted by using t-test and ANOVA. The results were considered as statistically significant if the p value was less than 0.05.

RESULTS

Demographic and social characteristics

The demographic and social characteristics of the study population are presented in Tables 1 and 2. Two-thirds of the subjects were below the age of 65 and almost all of the subjects were drug and alcohol-free, and most (79 %) were

Table 1: Demographic characteristics of the study population

Demographic characteristics (n=100)	N	%
Gender	*100*	*100.0*
Male	55	55.0
Female	45	45.0
Age	*100*	*100.0*
18-64 years old	63	63.0
≥65 years old	37	37.0
Ethnicity	*100*	*100.0*
Malay	38	38.0
Chinese	19	19.0
Indian	41	41.0
Others	2	2.0

Table 2: Social characteristics of the study population

Social characteristics	N	%
Smoking history	*100*	*100.0*
Smoker	10	10.0
Non-smoker	79	79.0
Ex-smoker	11	11.0
Alcohol consumption	*100*	*100.0*
Yes	5	5.0
No	95	95.0
Drug abuse	*100*	*100.0*
Yes	0	0.0
No	100	100.0
*Family history of T2DM**	*100*	*100.0*
Yes	8	8.0
No	92	92.0

** T2DM = type 2 diabetes mellitus.*

non-smokers. Most (92 %) of the subjects did not have a family history of T2DM.

Clinical characteristics

There were an increasing number of subjects with a longer duration of T2DM (Table 3). A total of 28.9 % had suffered from T2DM for > 20 years.

The most frequently encountered comorbidity among the study subjects was hypertension (Figure 1).

Table 3: Duration of type 2 diabetes mellitus among the study population

Duration of T2DM* (year, n=76)	N	%
<1	0	0.0
1-5	11	14.5
6-10	12	15.8
11-15	15	19.7
16-20	16	21.1
>20	22	28.9
Total	*76*	*100.0*

**T2DM = type 2 diabetes mellitus.*

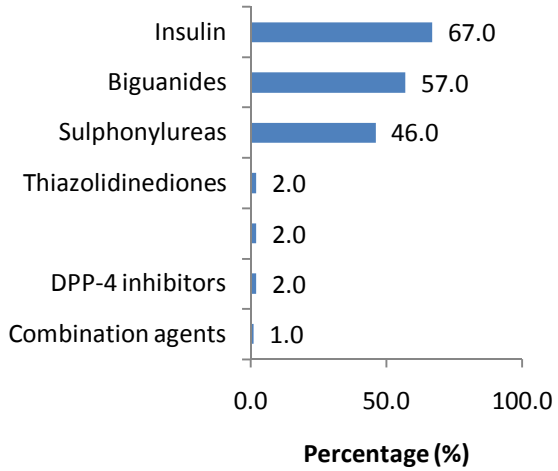

Figure 1: Types of antidiabetic medication used by the study subjects

Antidiabetic medication use

The majority of subjects (45.0 %) consumed only one antidiabetic agent, 36.0 % two and 19.0 % more than two. With regard to the types of antidiabetic medications used, the three most common types were insulin, biguanides, and sulfonylureas. Among these drug groups, insulin was the most utilized antidiabetic agent, with 67.0 % of the subjects taking insulin. The rates of biguanide and sulfonylurea use were 57.0 and

46.0 %, respectively. The other types of antidiabetic agents, such as thiazolidinediones, α-glucosidase inhibitors, DPP-4 inhibitors, and combination agents, were rarely being taken (Figure 2).

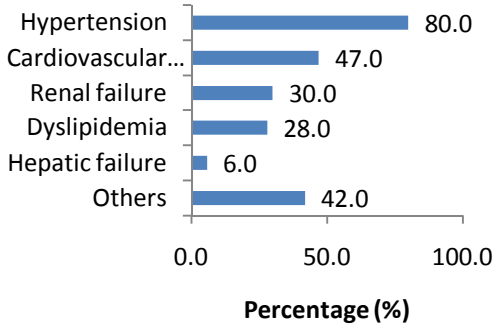

Figure 2: Distribution of comorbid conditions

Table 4 illustrates the number of patients prescribed a certain type of antidiabetic medication. Among the 67 insulin users, a combination of actrapid and insulatard was used by the majority of patients (88.0%). Regular metformin was utilized by 56 out of 57 biguanide users (98.2%), while 37 out of 46 sulfonylurea users (80.5%) were prescribed with gliclazide. Rosiglitazone, acarbose, sitagliptin, and janumet (sitagliptin and metformin) were the only thiazolidinedione, α-glucosidase inhibitor, DPP-4 inhibitor, and combination agents used, respectively, among the study subjects.

Use of Concurrent Medications

Statins were the most commonly prescribed concurrent medication, with 70.0% of subjects receiving statins. This was followed by aspirin (46.0%), ACE inhibitors (45.0%), and calcium channel blockers (44.0%). Beta blockers, diuretics, clopidogrel, ticlopidine, nitrates, and angiotensin receptor blockers were also in the top ten drug groups used by the study subjects. The distribution of the top ten concurrent medications used by the T2DM patients is summarized in Figure 3.

Table 4: Patients prescribed a certain type of antidiabetic medication

Antidiabetic type	N	%
Insulin	*67*	*100.0*
Actrapid + Insulatard	59	88.0
Mixtard	4	6.0
Lantus	2	3.0
Actrapid only	1	1.5
Insulatard only	1	1.5
Biguanides	*57*	*100.0*
Regular metformin	56	98.2
Extended-release metformin	1	1.8
Sulfonylureas	*46*	*100.0*
Gliclazide	37	80.5
Glibenclamide	7	15.2
Glipizide	2	4.3
Thiazolidinediones	*2*	*100.0*
Rosiglitazone	2	100.0
α-glucosidase inhibitors	*2*	*100.0*
Acarbose	2	100.0
DPP-4 inhibitors	*2*	*100.0*
Sitagliptin	2	100.0
Combination agents	*1*	*100.0*
Janumet	1	100.0

* DPP-4 = dipeptidyl peptidase-4

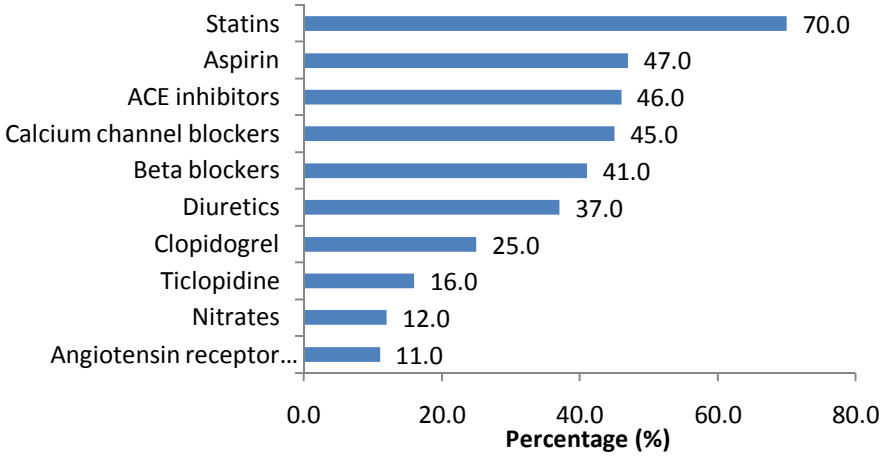

Figure 3: Concurrent use of medication among patients with type 2 diabetes mellitus (Patients may have more than one concurrent medication)

Among the 70 statin users, simvastatin was the most commonly used statin (82.9 %). Perindopril was the leading ACE inhibitor, with 40 out of 46 subjects (87.0 %) on ACE inhibitors using it. Amlodipine was used by 39 out of 45 subjects (86.5 %) on calcium channel blockers, making it the most popular calcium channel blocker. Metoprolol was the most prominent beta-blocker, with 20 out of 41 subjects (48.8 %) on beta-blockers using it. A breakdown of the drugs for indications other than T2DM is summarized in Table 5.

Table 5: Distribution of individual concurrent medications among patients with type 2 diabetes mellitus

Concurrent drug type and name	N	%
Statins	*70*	*100.0*
Simvastatin	58	82.9
Atorvastatin	9	12.9
Lovastatin	2	2.8
Rosuvastatin	1	1.4
ACE inhibitors	*46*	*100.0*
Perindopril	40	87.0
Lisinopril	3	6.5
Enalapril	2	4.3
Captopril	1	2.2
Calcium channel blockers	*45*	*100.0*
Amlodipine	39	86.5
Diltiazem	2	4.5
Felodipine	2	4.5
Nifedipine	2	4.5
Beta-blockers	*41*	*100.0*
Metoprolol	20	48.8
Atenolol	14	34.1
Bisoprolol	4	9.8
Carvedilol	2	4.9
Propanolol	1	2.4

Abbreviations: ACE, angiotensin-converting enzyme

Clinical Progress of T2DM

Qualitative Analysis

There were no significant associations between baseline FPG and recent FPG (p=0.634). There were also no significant associations between baseline A1c and recent A1c levels (p=0.408).

Quantitative Analysis

Initially, the normality of FPG and A1c levels were determined using Shapiro-Wilk Test. The mean ± S.D. for baseline FPG and recent FPG were 11.63 ± 5.25 mmol/L ($p < 0.001$) and 10.44 ± 5.71 mmol/L ($p < 0.001$) respectively. The baseline A1c and recent A1c were 9.30±2.95 ($p < 0.001$) and 8.76 ± 2.52 % ($p < 0.001$) respectively. It was determined that all levels had a p-value of < 0.05, indicating that the values are not normally distributed. However, for the purpose of this study, all of the parameters were assumed to be normally distributed.

We then compared the baseline and recent values using paired samples t-test. There were no significant differences (p = 0.239) between baseline (11.61 ± 5.15) and recent FPG (10.59±5.98) levels. Additionally, there were no significant differences (p=0.093) between baseline (9.45 ± 3.03) and recent A1c levels (8.74 ± 2.51).

Factors associated with response to antidiabetic medications

Hypertension

There is a significant association between hypertension and recent A1c levels (p = 0.011). Subjects with hypertension had lower recent A1c levels (8.45 ± 2.34) compared to subjects without hypertension (10.61 ± 2.91).

Sulfonylureas

There was a significant association between the use of sulfonylureas and recent A1c levels (p = 0.041). Subjects prescribed with sulfonylureas had lower recent A1c levels (8.11 ± 2.16) compared to subjects who were not prescribed with sulfonylureas (9.34 ± 2.71).

Beta-blockers

There was a significant association between the use of beta-blockers and recent A1c levels (p = 0.005). Subjects prescribed with beta-blockers had higher recent A1c levels (9.69 ± 2.74) compared to subjects who were not prescribed with beta-blockers (7.98 ± 2.05).

Baseline A1c levels

There was a significant association between baseline A1c and recent A1c levels (p<0.001). Subjects with normal baseline A1c levels had lower recent A1c levels (6.15±0.82) compared to subjects with abnormal baseline A1c levels (9.09±2.46).

Factors not associated with response to antidiabetic medications

All other parameters examined were not significantly different baseline A1c and recent A1c levels, shown as in Table 6, indicating that demographic, clinical, comorbidities and drug intakeare not significantly associated with recent A1c levels.

Table 4: Factors not significantly associated with recent A1c levels

Parameter	Recent A1c (%)		*P*-value
	Mean	S.D.	
Gender (n=70)			
Male (n=36)	8.76	2.68	0.999[a]
Female (n=34)	8.76	2.39	
Age (n=70)			
18-64 years old (n=43)	9.13	2.58	0.126[a]
≥65 years old (n=27)	8.17	2.37	
Ethnicity (n=70)			
Malay (n=28)	8.91	2.90	0.367[b]
Chinese (n=13)	7.86	2.44	
Indian (n=29)	9.01	2.15	
Smoking history (n=70)			
Smoker (n=8)	8.88	1.90	0.700[b]
Non-smoker (n=53)	8.63	2.47	
Ex-smoker (n=9)	9.40	3.43	
Alcohol drinking (n=70)			
Yes (n=3)	11.23	2.02	0.083[a]
No (n=67)	8.65	2.50	
Family history of T2DM (n=70)			
Yes (n=6)	8.23	2.57	0.598[a]
No (n=64)	8.81	2.54	
Duration of T2DM (n=57)			
1–5 (n=7)	9.30	2.27	
6–10 (n=10)	7.90	1.99	0.429[b]
11–15 (n=12)	8.01	3.00	
16–20 (n=12)	9.23	2.79	
>20 (n=16)	9.41	2.44	
Cardiovascular disease (n=70)			0.922[a]
Yes (n=35)	8.79	2.35	
No (n=35)	8.73	2.72	
Renal failure (n=70)			
Yes (n=19)	8.41	2.53	0.492[a]
No (n=51)	8.89	2.54	
Dyslipidemia (n=70)			
Yes (n=23)	8.76	2.45	0.996[a]
No (n=47)	8.76	2.59	
No. of diabetes medications (n=70)			
One (n=26)	8.65	2.83	0.832[b]
Two (n=26)	9.00	2.47	
More than two (n=18)	8.57	2.22	
Insulin (n=70)			
Yes (n=54)	9.06	2.62	0.063[a]
No (n=16)	7.73	1.92	
Biguanides (n=70)			
Yes (n=43)	8.88	2.35	0.604[a]
No (n=27)	8.56	2.81	
Statins (n=70)			
Yes (n=55)	8.73	2.54	0.880[a]
No (n=15)	8.85	2.56	
Aspirin (n=70)			
Yes (n=34)	8.59	2.17	0.581[a]
No (n=36)	8.92	2.84	
ACE inhibitors (n=70)			
Yes (n=35)	9.15	2.49	0.198[a]
No (n=35)	8.37	2.53	
Calcium channel blockers (n=70)			0.052[a]
Yes (n=35)	8.17	2.16	
No (n=35)	9.34	2.75	

*[a]Analyzed by using independent samples t-test; [b]analyzed by using one way ANOVA; *ACE = angiotensin-converting enzyme; T2DM = type 2 diabetes mellitus*

DISCUSSION

It was determined that there is a significant reduction in recent A1c levels in subjects with hypertension compared to subjects without hypertension. This may be an anomaly in the results, as previous reports showed that patients with hypertension tend to have higher blood glucose levels compared to those without hypertension [4, 5]. Ruggenenti and Whaley-Connell suggested that there is a correlation between elevated blood pressure and insulin resistance [6,7]. A possible reason for this anomaly is the relatively small sample size compared to other studies.

It was determined that there is a significant reduction in recent A1c levels in subjects prescribed with sulfonylureas compared to subjects not prescribed with sulfonylureas. Krentz & Bailey (2005) reported that monotherapy with sulfonylureas can reduce FPG and A1c levels by 2 – 4 mmol/L and 1 – 2 %, respectively [8].

Previous studies have shown that biguanides are similarly efficacious to sulfonylureas with respect to reducing A1c levels when compared to placebo [8, 9]. However, in the present study, A1c levels in patients prescribed with biguanides were higher than those not prescribed with biguanides. Potential reasons behind may be small sample size and different patient characteristics.

It was found that there is a significant increase in recent A1c levels in subjects prescribed with beta-blockers compared to subjects not prescribed with beta-blockers. In the present study, atenolol (48.8 %) and metoprolol (34.1%) were the most commonly prescribed beta-blockers, both of which are of the non-vasodilating type.

Fonseca (2010) reported that non-vasodilating beta-blockers are associated with glucose and lipid abnormalities because they reduce cardiac output without affecting peripheral vascular resistance [10]. Vasodilating beta-blockers, such as carvedilol and nebivolol, are reported to have less impact on insulin sensitivity and glycemic control, as well as reduce the risk of new onset diabetes [11]. Sander & Giles (2010) also recommended the use of vasodilating beta-blockers to decrease cardiovascular morbidity and mortality without exposing patients to undesirable side effects on glucose metabolism [12].

There is a significant increase in recent A1c levels in subjects with abnormal baseline A1c levels compared to subjects with normal baseline A1c levels. Subjects whose baseline A1c levels were well-controlled generally have a lower risk of therapeutic failure with diabetes medications. Turner *et al*. (1999) noted that patients who are more hyperglycemic have a lower probability of achieving glycemic targets [13].

Study limitation

This study only took into account information that is readily available from medical records. Thus, some other factors that may affect the response of patients to antidiabetic medications, but were not available in the medical records, may not have been considered.

CONCLUSION

Although the recent FPG and A1c levels were lower compared to their baseline values, their reductions failed to achieve significance. Hypertension, sulfonylureas, beta-blockers, and baseline A1c levels were significantly associated with a response to antidiabetic medications. In conclusion, further optimization with respect to the pharmacotherapy of T2DM is warranted to ensure that the diabetic condition of patients is well-controlled.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to report.

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REFERENCES

1. *Ministry of Health Malaysia. Clinical Practice Guidelines on the Management of Type 2 Diabetes Mellitus 4th ed. 2009. Available from: URL: http://www.acadmed.org.my/index.cfm?&menuid=67*
2. *Pharmaceutical Services Division and the Clinical Research Centre. Malaysian Statisticson Medicine 2007 2007. Available from: URL: http://www.pharmacy.gov.my/aeimages//File/MSOM2007_2.pdf*
3. *WMA. Declaration of Helsinki. Ethical principles for medical research involving human subjects. 59th WMA General Assembly. 2008. Seoul. Available from: URL: http://www.wma.net/en/30publications/10policies/b3/17c.pdf*
4. *Gress TW, Nieto FJ, Shahar E, Wofford MR, Brancati FL. Hypertension and antihypertensive therapy as risk factors for type 2 diabetes mellitus. N Engl J Med 2000; 342: 905–912.*
5. *Kumar NL, Deepthi J, Rao YN, Deedi MK. Study of lipid profile, serum magnesium and blood glucose in hypertension. Biol Med 2010; 2: 6–16.*
6. *Ruggenenti P, Cattaneo D, Loriga G, Ledda F, Motterlini N, Gherardi G, Orisio S, Remuzzi G. Ameliorating hypertension and insulin resistance in subjects at increased cardiovascular risk: Effects of acetyl-L-carnitine therapy. Hypertension 2009; 54: 567–574.*
7. *Whaley-Connell A, Sowers JR. Hypertension and insulin resistance. Hypertension 2009; 54: 462–464.*
8. *Krentz AJ, Bailey CJ. Oral antidiabetic agents: current role in type 2 diabetes mellitus. Drugs 2005; 65: 385–411.*
9. *Bennett WL, Maruthur NM, Singh S, Segal JB, Wilson LM, Chatterjee R, Marinopoulos SS, Puhan MA, Ranasinghe P, Block L, Nicholson WK, Hutfless S, Bass EB, Bolen S. Comparative effectiveness and safety of medications for type 2 diabetes: An update including new drugs and 2-drug combinations. Ann Intern Med 2011; 154: 602–613.*
10. *Fonseca VA. Effects of β-blockers on glucose and lipid metabolism. Curr Med Res Opin 2010; 26: 615–629.*
11. *Deedwania P. Hypertension, dyslipidemia, and insulin resistance in patients with diabetes mellitus or the cardiometabolic syndrome: Benefits of casodilating β-blockers. J Clin Hypertens 2011; 13: 52–59.*
12. *Sander GE, Giles TD. Thiazide diuretics and β-blockers in the treatment of hypertension in diabetes mellitus. J Clin Hypertens 2011; 13: 296–300.*
13. *Turner RC, Cull CA, Frighi V, Holman RR. Glycemic control with diet, sulfonylurea, metformin, or insulin in patients with type 2 diabetes mellitus: progressive requirement for multiple therapies (UKPDS 49). UK Prospective Diabetes Study (UKPDS) Group. JAMA 1999; 281: 2005–2012.*