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THE ROLE OF PHARMACISTS MEDICATION THERAPY REVIEW ON IMPROVING THERAPEUTIC EFFECTIVENESS, QUALITY OF LIFE, AND DRUG RELATED PROBLEMS IN TYPE 2 DIABETES MELLITUS PATIENTS : A SYSTEMATIC REVIEW

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ABSTRACT

Background: Diabetes mellitus (DM) is one of the metabolic disease that requires long term and continuous control of the medical staff. In 2015, there were 415 million people with DM in the world that predicted to increase to 642 million in 2040. So that the disease became important to focus as a world health problem. Pharmacists have a role to be involved in the management of blood glucose in patients by doing medication therapy review (MTR) before pharmaceutical care intervention. Not all pharmacists do MTR before doing pharmaceutical care, because there is no exact data on how well the MTR can affect the effectiveness of DM therapy.
Objective: The aim of this study was to evaluate how far MTR can improve the changes in treatment outcomes, quality of life (QoL), and drug related problems (DRP) in patients with type 2 DM through a systematic review.
Methods: Research articles that related to pharmacist's MTR were collected from 2006-2014. Google Scholar and two electronic databases i.e. PUBMED and Science Direct were used. After the articles were collected, the next step was the selection of eligible manuscripts, data extraction and synthesis.
Result: Eleven articles were included, involving 1738 patients. MTR carried out by pharmacists, can significantly improve treatment outcomes, QoL, and DRP ($p< 0.05$). MTR was found reduce 30-40% of potential DRP.
Conclusion: MTR is one effort that can be done by a pharmacist to accelerate the achievement of therapeutic goals, improve the QoL, and reduce the rate of DRP in DM patients.
Keywords: Medication Therapy Review, Type 2 Diabetes Mellitus, Effectiveness of Diabetes Therapy, Drug Related Problem, Quality of Life
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INTRODUCTION

Diabetes mellitus is a metabolic disease with characteristics of hyperglycemia caused by dysfunction of insulin production, insulin resistance or both.[1] In 2015, there were 415 million people with diabetes in the world and the number is expected increases to 642 million in 2040.[2] Uncontrolled blood sugar profiles of diabetic patients potentially increase the risk of heart disease, diabetic neuropathy, diabetic retinopathy and diabetic nephropathy.[3] Complications of diabetes mellitus can be prevented or minimized through effective blood glucose management.[3]

Pharmacists have a role to be involved in the management of blood glucose in diabetic patients by conducting a review of patient treatment, monitoring treatment, and ensuring the effectiveness and safety of patient treatment.[3,4] Medication therapy review (MTR) is one of the cores in medication therapy management (MTM) which is important to be carried out by pharmacists to help achieve the outcome of therapy, improve the quality of life (QoL), and reduce drug related problems (DRP) for patients with diabetes.[5,6]

MTR is a process of collecting patient information systematically and specifically such as identifying DRP, developing a priority list of DRP, assess the QoL and making plans to address them. A comprehensive MTR, ideally carried out by a pharmacists.[3,5,6] In this systematic review, the effect of MTR in pharmaceutical care would be examined to show the improvements on therapeutic outcomes, QoL, and DRP of patients with type 2 DM. The results of this study will illustrate how well the outcome of treatment for diabetic patients treated by pharmacists through MTR intervention.

MATERIAL AND METHODS

This systematic review analyzed the impact of MTR in pharmaceutical care on improving the outcome of therapy, QoL, and DRP of patients with type 2 DM.

Study identification

Google Scholar and two electronic databases i.e. PUBMED (2006-2014) and Science Direct (2006-2014) were initially searched from September 2018 to April 2019. Search terms included 'Medication Therapy Review', 'Pharmaceutical Care', 'Type 2 Diabetes Mellitus', 'Drug Related Problem', Quality of Life' and 'Effectiveness of Diabetes Therapy.

Eligibility criteria

The title and abstract of the original article was assessed by three independent reviewers. The first step was screening abstracts of the articles obtained. If the abstract was felt to be in accordance with the topic, the full text would be downloaded. If there were differences in article eligibility opinions between reviewers, the problem was resolved through discussion until consensus was reached.

All randomize control trial (RCT) studies that provide pharmaceutical care interventions preceded by the MTR process by the pharmacists would be downloaded in full text. RCT studies that looked at the therapeutic effectiveness of adult patients aged 20 to > 65 years with type 2 diabetes, such as changes in value of HbA1C, blood glucose (fasting glucose, prandial glucose, random glucose), blood pressure (BP), body mass index (BMI), lipid profile (total cholesterol, HDL, LDL, TG); DRP (adherence, dose related problems, drug interactions, adverse drug events, and medication errors); and QoL of patients with diabetes were included in the inclusion criteria in this study.

The exclusion criteria in this study were pharmaceutical care interventions without going through the MTR process, the outcome observation period was less than 4 months, and the MTR intervention was not carried out by pharmacists.

Data extraction and synthesis

Data extraction was conducted by one reviewer using standard Microsoft Excel and Word software. After the data were successfully extracted, another reviewers conducted an assessment independently. The review process was not blind.

Major revisions are carried out through the discussion stage, with all reviewers to obtain an agreement.

Data extraction was made in two stages. The first stage was the extraction characteristics of article's data, consisting of the author's name along with the year of publication, county, research setting, method, study design, follow-up duration, intervention patients, intervention control, and outcomes measure. Extraction of the second stage was done by presenting the findings of observations in the form of diabetes therapy outcomes, QoL, and DRP. The subsequent data extraction contains information on the results of the intervention briefly, and the statistical differences between the intervention group and the control group.

RESULT

Search Result

In the period of September, to November 2018 there were 233 RCT articles found. There were 28 articles from Google Scholar, 199 articles from PUBMED, and 6 articles from Science Direct (Figure 1). After screening and filtering, there were 23 duplicate articles, 117 articles did not fit the study criteria, and 33 articles have the potential to be further evaluated based on the abstract. Furthermore, 15 articles were not downloaded in full text because it was known that MTR was not carried out by pharmacists (carried out by nurses and other health workers). The eligibility assessment was carried out on 18 articles downloaded in full text. There were 7 articles that excluded in the eligibility assessment stage because there were confusion and unclear description of the DRP outcomes and the form of the MTR that had been done. Thus, there were 11 articles included for analysis in this study.

Studies characteristics

All articles that analyzed were RCTs from 2006 to 2014. Articles included in the study came from several countries such as USA[7,8], Australia[9], Netherland[10], United Emirates[11], UK[12], Jordan[13], Brazil[14], Stockholm[15], Malaysia[16], and Denmark[17]. Intervention settings were in hospitals and communities, with the total number of subjects analyzed being 1738 patients with type 2 DM. Patients in this study globally were adults in the range of 20 to > 65 years, who were given an intervention in the form of MTR before starting pharmaceutical service. The shortest duration of follow-up was 4 months, and the longest was 12 months. The outcomes measured in this study were the effectiveness of diabetes therapy, DRP, and QoL. At least 1 of the 3 outcomes above must be contained in the article. A detailed description of the characteristics of the articles in this study can be seen in table 1.

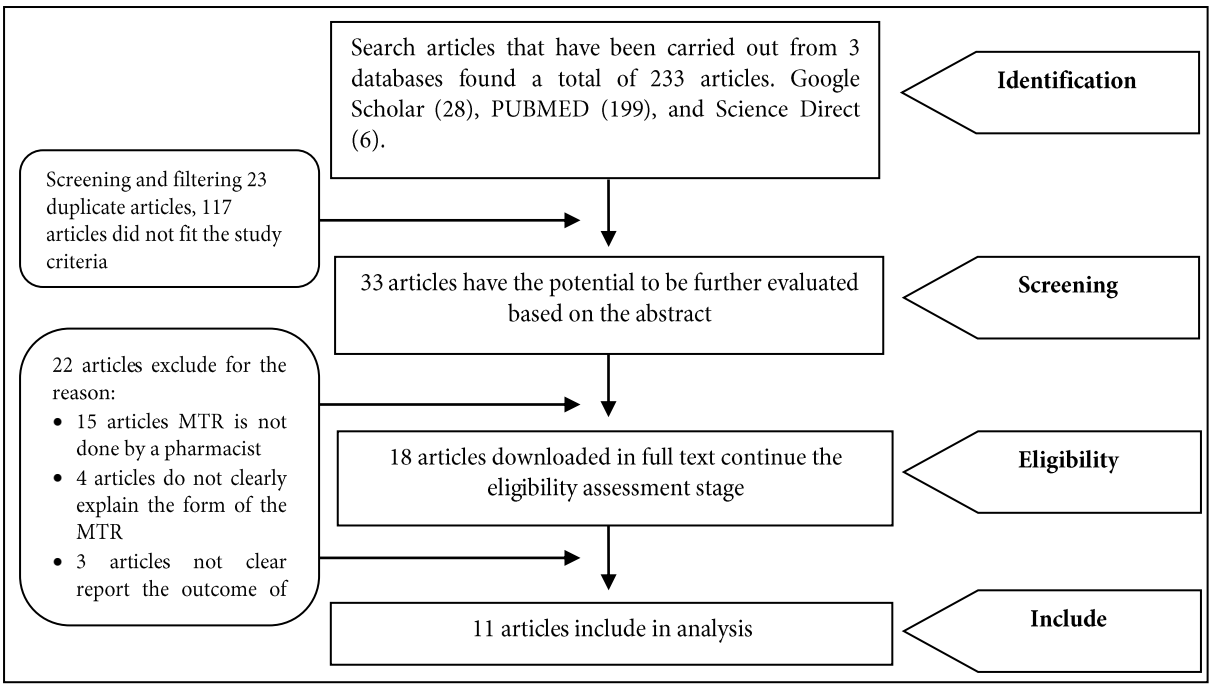

Figure 1. PRISMA diagram of the article selection process

Description MTR was done by pharmacists

In this study, MTR intervention carried out by pharmacists through a review process that contains information on prescription and non-prescription drugs, herbal products, and other food supplements used by patients before subsequently providing pharmaceutical services.[8,14,16] During the review process pharmacists can assess drug-related problems, including compliance, and work with patients, doctors, or other professional health personnel to make the right choices to resolve the identified problem.[7,9,11]

In general, the MTR can be started by interviewing patients to collect data including demographic information, general health status, activity status, medical history, medication history, immunization history, and patient's thoughts or feelings regarding his condition and use of drugs.[4,6,18] After that, the

review process can be continued by assessing all relevant clinical information such as physical health and overall health status of the patient, including the current disease or condition and previous illness or condition and assessing, identifying, and compiling a list of priority DRP.[4,18]

OUTCOME EVALUATION

1. MTR improves effectiveness of DM therapy

Based on 11 articles included, there were nine articles evaluating the effect of MTR on the effectiveness of DM therapy.[7–9,11–14,16,17] The therapeutic outcomes measured include: HbA1C, FBG (fasting blood glucose), RBG (random blood glucose), SBP (systolic blood pressure), DBP (diastolic blood pressure), TC (total cholesterol), LDL (low density lipoprotein), HDL (high density lipoprotein), TG (triglyceride), body weight, and BMI (body mass index)

In the HbA1C outcome, there are 8 articles that evaluate it.[7–9,11–14,16] All articles stated that there was a significant ($p< 0.05$) reduction in HbA1C in the intervention group compared to the control group.[7–9,11–14,16] Whereas in the outcome of the blood pressure, lipid profile, and BMI, most of them stated that there were significant changes even though there were several articles stating that they were not significantly different.[7–9,11–14,16,17] Outcome results of the article in this study in detail can be seen in table 2.

HBA1C is the most important outcome to describe the therapeutic goal of patients with diabetes.[1,5] If the blood sugar profile is controlled, the risk of macrovascular and microvascular complications can be prevented or slowed down.[3,4] Other outcomes such as blood pressure, lipid profile, and BMI are supporting parameters used to evaluate comorbid which is commonly present in patients.[4] Overall, the MTR carried out by pharmacists before conducting pharmaceutical services can accelerate the achievement of therapeutic goals in DM patients.

2. MTR improve the QoL

There are 5 articles that evaluate QoL.[7,9,11,12,17] The QOL instruments used included DQOL, HRQoL-5D, and HRQoL SF36. The results showed that the MTR intervention gave a tendency for a significant increase in the QoL score compared to the control ($p <0.05$).[7,9,11,12,17] This illustrates that there is an increase in the quality of life of DM patients when given MTR intervention by a pharmacist. The QoL results of article in this study in detail can be seen in table 2.

The World Health Organization (WHO) defines quality of life as an individual's perception from the perspective of individual life in the context of culture and the life values of an individual.[19] The definition contains four domains in which includes quality of life from aspects of physical, psychological, social, and environmental health.[19,20] Diabetes is a chronic disease that requires lifelong therapy, the poor quality of life in DM patients will affect the success of treatment.[2] Thus efforts to improve the quality of life of DM patients will be able to maintain the behavior of patients to continue to apply the therapy optimally.[4,20]

3. MTR improve the DRP events

The DRP evaluated in the article in this study generally consisted of 6 main problems, among others: wrong in determining the dosage of the drug (too high / low), there were indications that had not been treated, wrong choice of drugs (dosage form, and excessive drug therapy), adverse drug reaction (ADR), drug interactions, and compliance with drug therapy.[8,10,11,13–17] A total of 8 articles evaluated DRP outcomes.[8,10,11,13–17] Broadly speaking, the provision of MTR interventions can reduce 30-40% of potential DRP.[10,14] In some articles adherence to drug therapy was the focus of the study because adherence was one of the predictors of treatment failure.[11,13–17] Non-compliance with drug therapy dropped significantly ($p <0.05$) in the intervention group compared with controls.[8,10,11,13–17] This shows that compliance will increase if the pharmacists conducts MTR first to find out the problems of therapy non-compliance. The DRP results of article in this study in detail can be seen in table 2.

DRP is a matter that must be a concern for a pharmacists.[4] If the DRP appears, pharmacists must be in the first line to detect it and find solutions to its limitations.[5,6] Through the MTR, a pharmacist will be able to identify the DRP, develop a priority list of drug-related problems, and make plans to deal with them quickly and precisely.[3,5,6]

DISCUSSION

Medication therapy review (MTR) is one of the core elements in medication therapy management (MTM).[6] In this study it was found that the success of pharmaceutical services was determined by how deeply a pharmacist was able to recognize the patient's clinical condition holistically.[5,6] Through MTR, pharmacists can earlier identify drug-related problems in patients, so pharmacists can create optimal Medication Action Plans (MAP). Thus, the desired outcome of therapy will be more easily achieved.[5,6,12,13]

There are no standard rules / steps for conducting MTR.[6] Every pharmacists generally have their own way to do a review process. As long as the results of the review are useful in preparing the MAP, the process is recommended.[6,18] The MTR should include minimal information on drug-related problems, develop a priority list of drug-related problems, and make plans to address them.[3–5]

MTR in its implementation will have more benefits if implemented in full in the MTM program.[6,18] MTM is a service design for patients that focuses on collaboration between pharmacists, doctors, nurses, and health workers and optimizes communication between patients and the health care team with the aim of achieving therapeutic effectiveness that is fast, precise, optimal, and safe for patients.[6,18] In general, the design of MTM services is categorized into 5 elements, namely medication therapy review (MTR), patients prescription record (PPR), medication action plan (MAP), intervention or referral (IoR), documentation and follow-up.[6,18]

In this systematic review, there are several limitations, such as not all articles analyzed measure three outcomes in the form of effectiveness, QoL, and DRP. Another limitation, the authors did not succeed in collecting uniform forms of MTR intervention for the entire article in this study. Thus, further research can consider limitations in this study.

CONCLUSION

Medication therapy review (MTR) carried out by pharmacists before implementing pharmaceutical care, can accelerate the achievement of therapeutic outcomes, improve the QoL, and reduce DRP rates in patients with type 2 DM. Pharmacists are recommended to start doing MTR first before giving intervention to patients, so that the problems encountered by patients can be identified early and planning to deal with problems can be done properly and wisely.

ABBREVIATIONS USED

HbA1c= glycosylated hemoglobin; RBG= random blood glucose; BMI= body mass index; DBP= diastolic blood pressure; QoL= quality of life; DRP= drug-related problems; FBG= fasting blood glucose; HDL= high-density lipoprotein cholesterol; LDL= low-density lipoprotein cholesterol; NA= not available; PCP= primary care provider; SBP= systolic blood pressure; TC= total cholesterol; TG= triglycerides; IG= intervention group; CG= Control Group; RCT= Randomize Control Trial; T2DM= Type 2 Diabetes Mellitus; DM= Diabetes Mellitus; n = subject / patients; ADEs= Adverse drug events; ADR= Adverse drug reaction; NR= not reported; HRQoL= health related quality of life; DQoL= diabetes quality of life; Diff.= difference; NAT= Need additional therapy; UDT= Unnecessary drug therapy; Cont.= continue.

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Table 1. Characteristics of articles in the study

Author, Year	Country, Research Setting	Subject / Patients	Method, Study Design	Follow Up Duration	Patients Intervention	Control Intervention	Outcome Measures
Scott et al. 2006[7]	USA / Community health center	Adult age range between >20 and 69 years with T2DM.	RCT, Total 131 patients (n=64 IG, n=67 CG).	9 months	Medication review by pharmacist, education on diabetes, self-monitoring, self-care, and pharmacotherapy recommendations.	Standard diabetes care.	Effectivity: HbA1c, SBP, DBP, LDL, HDL, BMI, body weight, QOL (DQOL).
Krass et al. 2007[9]	Australia / Community pharmacies	Adult age with the mean age 62 ± 11 years.	RCT, Total 289 patients (n=149 IG, n=140 CG).	6 months	Medication review by pharmacist including medication review, RBG, DM education, and lifestyle.	Usual medical care.	Effectivity: HbA1C, SBP, DBP, TC,TG, BMI HRQoL EQ-5D.
Mazroui et al. 2009[11]	United Emirates/ Military hospital	Adult age range between 35 and > 65 years with T2DM.	RCT, Total 234 patients (n=117 IG, n=117 CG).	12 month	Medication therapy review were done by discussions with PCP regarding drug therapy by pharmacist; education on disease and medication.	Usual care offered by military hospital.	Effectivity : HbA1C, FBG, SBP, DBP, TC, LDL, HDL, TG, BMI. DRP : Medication adherence QOL (QOL SF36).
Thijs et al. 2009[10]	Netherland / 16 Community pharmacies	Elderly / Age ≥ 65 years using six or more medications and chronic diseases.	RCT, Total n=98 IG, n=98 CG. DM, n=33 IG, n=24 CG.	4 month	Medication therapy review was performed to review ten types of potential DRP into the following three categories: patient-related potential DRP, prescriber-related potential DRP and drug related potential DRP.	Usual care offered by community pharmacies practice.	The primary outcome : change in the number of potential DRP.
Jacob et al. 2012[8]	USA / General Internal Medicine Clinic	Adult age >18 years. Mean of age 63 ± 11 years with T2DM.	RCT, Total 164 patients (n=72 IG, n=92 CG).	12 month	Pharmacist did a comprehensive medication review, physical assessment, laboratory tests (blood check), reviewing, modifying, and monitoring diabetes medication therapy.	Usual care by general internal medicine clinic practitioner.	Effectivity : HbA1c, SBP, DBP, LDL, BMI. DRP : Medication use, microvascular parameters screening for diabetes and it's comorbidities.
Ali M et al. 2012[12]	UK / Community pharmacies	Adult age range between 45 and > 65 years with T2DM.	RCT, Total n = 46 (n=23 IG, n=23 CG).	12 month	Medication therapy review were done by reviewing drug use review by pharmacist, education diabetes diseases and its complications.	Usual care by practitioner, nurse and Pharmacist.	Effectivity : HbA1c, RBG, SBP, DBP, TC, LDL, HDL, TG, BMI. QOL.
Jarab et al. 2012[13]	Jordan / Teaching Hospital, Diabetes Clinic	Adult age with the mean of age 65 ± 10 years with T2DM.	RCT, Total n =156 (n=77 IG, n=79 CG).	6 months	Intervention were done by reviewing of medicine prescribed treatment and diabetic life style modification.	Usual care by diabetes clinic staff (medical and nursing staff).	Effectivity : HbA1c, FBG, SBP, DBP, TC, LDL, HDL, TG, BMI, DRP: Medication adherence.
Author, Year	**Country, Research Setting**	**Subject / Patients**	**Method, Study Design**	**Follow Up Duration**	**Patients Intervention**	**Control Intervention**	**Outcome Measures**
Mourão et al.	Brazil / Primary	Adult age ≥ 18	RCT, Total n = 100	6 months	Medication review by pharmacist, DRP	Usual care by	Effectivity : HbA1C, FBG, SBP,

2013[14]	health care	years with the mean age of this study was 61 ± 10 years with T2DM.	(n=50 IG, n=50 CG).		identification, education on diabetes, non-pharmacological and pharmacological treatments evaluation.	primary health care.	DBP, TC, LDL, HDL, TG, BMI, DRP : Need additional drug, unnecessary drug, ineffective drug, dose problem, ADR, & non compliance.
Lenander et.al 2014[15]	Stockholm / primary care centre	Elderly / Age ≥ 65 years with five or more medications.	RCT, Total n= 107 IG, n=102 CG. DM, n=26 IG, n=28 CG.	12 month	Medication therapy review was performed by a certified geriatrics pharmacist. They were checked for prescriptions, drug indications, and plans for evaluation.	Usual care offered by primary care center.	DRP event: ADEs, wrong drug, adherence, dose problem (too high/low), need additional therapy, unnecessary drug therapy.
Chung et.al 2014[16]	Malaysia / Teaching Hospital	Adult age range between 21 and 75 years with T2DM.	RCT, Total n = 241 (n=120 IG, n=121 CG).	12 month	Medication review by pharmacist, DRP evaluation (adherence), education on diabetes and their comorbidities.	Usual care by teaching hospital practitioner.	Effectivity : HbA1c & FBG DRP: Inappropriate adherence.
Kjeldsen et al. 2014[17]	Denmark / Community pharmacies	Adult age >18 years with the mean age of this study was 63 ± 8 years with T2DM.	RCT, Total n = 172 (n=70 IG, n=102 CG).	6 months	Medication therapy review by pharmacist, adherence screening, patient education diabetes mellitus and its comorbidities, feedback, follow up to PCP, and referral to other health services.	NR	Effectivity : BG, SBP, QOL DRP: Disease knowledge, medication non-adherence.

Table 2. Outcome results of article in this study

Author, Year	Therapeutic Effectiveness		Quality of Life		Drug Related Problems (DRP)	
	Result	Difference Between Groups	Result	Difference Between Groups	Result	Difference Between Groups
Scott et al. 2006[7]	1. HbA1C (%) = IG baseline 8.8 to 7.08 (change -1.7). CG baseline 8.7 to 8.0 (change -0.7). 2. SBP (mmHg) = IG baseline 130 to 126.6 (change -3.4). CG baseline 130.7 to 132.8 (change +2.1). 3. DBP (mmHg) = IG baseline 73.9 to 75.9 (change -3.4). CG baseline 79.6 to 78.2 (change -1.4). 4. LDL (mg/dL)= IG baseline 116.1 to 96.7 (change -19.5). CG baseline 120.5 to 112.3 (change -8.2). 5. HDL (mg/dL)= IG baseline 41.3 to 42.9 (change +1.6). CG baseline 41.5 to 42.4 (change +0.7). 6. BMI (kg/m^2)= IG baseline 36.4 to 36.0 (change -0.4). CG baseline 35.9 to 35.7 (change -0.2). 7. Body Weight (lbs)= IG baseline 225.4 to 221.3 (change -4.0). CG baseline 217.5 to 214.9 (change -2.6).	1. HbA1C = Diff. -1% (p=0.003) sig. 2. SBP = Diff. -5.5 mmHg (p=0.023) sig. 3. DBP = Diff. -2.0 mmHg. (not sig). 4. LDL = Diff. -11.2 mg/dL (p=0.012) sig. 5. HDL = Diff. +0.7 mg/dL. (not sig). 6. BMI= Diff. -0.2 kg/m^2 (not sig). 7. Body Weight = Diff. -1.4 lbs (not sig).	1. Health level (score)= IG baseline 39 to 54 (change +15). CG baseline 25.9 to 30.8 (change +4.9). 2. Satisfaction (score)= IG baseline 63.7 to 77.4 (change +13.7). CG baseline 57 to 63.4 (change +6.4). 3. Impact (score)= IG baseline 70.5, to 77.2 (change +6.7). CG baseline 66.5 to 68.3 (change +1.8). 4. Worry about disease (score)= IG baseline 66.5 to 76.6 (change +10.1). CG baseline 68.2 to 66.7 (change -1.5). 5. Worry about social and vocational issues (score)= IG baseline 67.3 to 75.5 (change +8.2). CG baseline 67.0 to 78.3 (change +11.3). 6. Total DQOL (score)= IG baseline 262 to 286.4 (change +24.4). CG baseline 232.5 to 247.3 (change +14.8).	1. Health level= Diff. +10.1 (p=0.002) sig. 2. Satisfaction= Diff. +7.6 (p=0.0007) sig. 3. Impact= Diff. +4.9 (p=0.002) sig. 4. Worry about disease= Diff. +10.1 (p=0.002) sig. 5. Worry social and vocational issues= Diff. -3.1 (p = NA). 6. Total DQOL Score = Diff. +9.6 (p<0.05) sig.	NA	NA
Krass et al. 2007[9]	1. HbA1C (%)= IG baseline 8.9 to 7.9 (change -1.0). CG baseline 8.3 to 8.0 (change -0.3). 2. SBP (mmHg)= IG baseline 135 to 133 (change -2.0). CG baseline 133 to 135 (change +2.0). 3. DBP (mmHg)= IG baseline 79 to 77 (change -2.0). CG baseline 77 to 76 (change -1.0). 4. TC (mmol/L)= IG baseline 4.9 to 4.7 (change -0.2). CG baseline 4.9 to 4.7 (change -0.2). 5. TG (mmol/L)= IG baseline 2.0 to 1.8 (change -0.2). CG baseline 1.8 to 1.7 (change -0.1). 6. BMI (kg/m^2)= IG baseline 31.4 to 31.1 (change -0.3). CG baseline 31.3 to 31.1 (change -0.2).	1. HbA1C= Diff. -0.7% (p<0.01) sig. 2. SBP= Diff. -4 mmHg (p=0.060) sig. 3. DBP= Diff. -1.0 mmHg (p=0.52) not sig. 4. TC= No diff. (p=0.85) not sig. 5. TG= Diff. -0.1 mmol/L (p=0.39) not sig. 6. BMI= Diff. -0.1 kg/m^2 (p=0.37) not sig.	HRQoL WQ-5D: 1. Utility (score)= IG baseline 0.8 to 0.8 (no change). CG baseline 0.8 to 0.8 (no change). 2. Health state (scale)= IG baseline 66.3 to 71.6 (change +5.3). CG baseline 72.3 to 73.3 (change +1.1).	1. Utility (score)= No Diff. (p=0.07) not sig. 2. Health state (scale): Diff. +4.3 (p=0.02) sig.	NA	NA
Author, Year	**Therapeutic Effectiveness**		**Quality of Life**		**Drug Related Problems (DRP)**	
	Result	**Difference**	**Result**	**Difference**	**Result**	**Difference**

		Between Groups		**Between Groups**		**Between Groups**
Mazroui et al. 2009[11]	1. HbA1C (%)= IG baseline 8.5 to 6.9 (change -1.6). CG baseline 8.4 to 8.3 (change -0.1). 2. FBG (mmol/L)= IG baseline 10.83 to 7.78 (change -3.05). CG baseline 10.26 to 9.48 (change -0.78). 3. SBP (mmHg) = IG baseline 131.4 to 127.2 (change -4.5). CG baseline 132.6 to 132.1 (change -0.5). 4. DBP (mmHg) = IG baseline 85.2 to 76.3 (change -8.9). CG baseline 83.9 to 84.1 (change +0.2). 5. TC (mmol/L) = IG baseline 5.26 to 4.47 (change -0.79). CG baseline 5.27 to 5.32 (change +0.5). 6. LDL (mmol/L) = IG baseline 3.55 to 3.04 (change -0.51). CG baseline 3.48 to 3.61 (change +0.13). 7. HDL (mmol/L) = IG baseline 1.20 to 1.32 (change +0.12). CG baseline 1.19 to 1.20 (change +0.01). 8. TG (mmol/L) = IG baseline 1.60 to 1.25 (change -0.35). CG baseline 1.55 to 1.74 (change +0.19). 9. BMI (kg/m^2) = IG baseline 28.34 to 27.29 (change -1.05). CG baseline 27.98 to 27.99 (change -0.01).	1. HbA1C = Diff. -1.5% (p<0.001) sig. 2. FBG= Diff. -2.27 mmol/L (p<0.001) sig. 3. SBP= Diff. -4.0mmHg (p<0.001) sig. 4. DBP= Diff. -9.1 mmHg (p<0.001) sig 5. TC= Diff. -1.29 mmol/L (p<0.001) sig 6. LDL= Diff. -0.64 mmol/L (p<0.001) sig 7. HDL= Diff. +0.121 mmol/L (p<0.001) sig 8. TG= Diff. -0.54 mmol/L (p<0.001) sig 9. BMI= Diff. -1.04 kg/m^2 (p<0.001) sig	QOL SF36: 1. Bodily pain (score)= IG baseline 43.2 to 66.7 (change +23.5). CG baseline 52.8 to 45.9 (change -6.9). 2. General health (score)= IG baseline 67.8 to 77.6 (change +9.8). CG baseline 66.6 to 69.2 (change +2.6). 3. Mental health (score)= IG baseline 60.4 to 71.5 (change +11.1). CG baseline 64.8 to 60.9 (change +3.9). 4. Physical functioning (score)= IG baseline 40.3 to 62.4 (change +22.1). CG baseline 49.3 to 48.0 (change -1.3). 5. Role emotional (score)= IG baseline 31.7 to 60.1 (change +28.4). CG baseline 40.0 to 48.8 (change +8.8). 6. Role physical (score)= IG baseline 37.3 to 67.1 (change +29.8). CG baseline 42.7 to 46.9 (change +4.2). 7. Social functioning (score)= IG baseline 66.6 to 87.2 (change +20.6). CG baseline 74.4 to 66.9 (change -7.5). 8. Vitality (score)= IG baseline 49.7 to 63.6 (change +13.9). CG baseline 55.1 to 49.9 (change -5.2).	1. Bodily pain= Diff. +30.4 (p<0.001) sig. 2. General health = Diff. +7.2 (p<0.001) sig. 3. Mental health= Diff. +7.2 (p<0.001) sig. 4. Physical functioning= Diff. +23.4 (p<0.001) sig. 5. Role emotional = Diff. +19.6 (p<0.001) sig. 6. Role physical= Diff. +25.6 (p<0.001) sig. 7. Social function = Diff. +28.1 (p<0.001) sig. 8. Vitality=Diff. +19.1 (p<0.001) sig.	Medication non-adherence (%)= IG baseline 48.3 to 21.4 (reduce 26.9). CG baseline 49.1 to 32.5 (reduce 16.6).	Non-adherence= Diff.10.3% (p<0.05) sig.
Thijs et al. 2009[10]	NA	NA	NA	NA	Number of potential DRPs = overall IG baseline 4.13 to 3.29 (reduce 0.84/20.3%). CG baseline 3.77 to 3.62 (reduce 0.15/4%).	Potential DRPs = Diff. -0.69/ -16.3% (95%CI:-24.3 to -8.3) sig.
Jacob et al. 2012[8]	1. HbA1C (%)= IG baseline 9.5 to 7.7 (change -1.8). CG baseline 9.2 to 8.4 (change -0.8). 2. SBP (mmHg)= IG baseline 142.5 to 132.5 (change -10). CG baseline 134.8 to 135.4 (change +0.6). 3. DBP (mmHg)= IG baseline 79.4 to 72.0 (change -7.4). CG baseline 78.3 to 77.6 (change -0.7).	1. HbA1C= Diff. -1.0% (p=0.003) sig. 2. SBP= Diff. -10.6 mmHg (p=0.223) not sig. 3. DBP= Diff. -6.7 mmHg (p=0.001) sig.	NA	NA	1. Medication use= IG increase 1.2%, CG increase 0.9% from baseline. 2. Microvascular parameters and it's comorbidities : Retinopathy =IG 97%; CG 83%; Neuropathy=IG 93%; CG 77%; Nephropathy= IG 96%; CG 62%.	1. Medication use= p< 0.05 sig. 2. Retinopathy: p=0.002 sig.; neuropathy: p=0.009 sig.; nephropathy: p=0.001 sig.
Author, Year	**Therapeutic Effectiveness**		**Quality of Life**		**Drug Related Problems (DRP)**	
	Result	**Difference Between Groups**	**Result**	**Difference Between Groups**	**Result**	**Difference Between Groups**

Jacob et al. 2012[8] (Cont.)	4. LDL (mg/dL)= IG baseline 121.5 to 93.7 (change -27.8). CG baseline 115.1 to 105.1 (change -10). 5. BMI (kg/m^2)= IG baseline 32.8 to 33.2 (change +0.4). CG baseline 31.8 to 31.6 (change -0.2).	4. LDL= Diff. -17.8 mg/dL (p=0.010) sig. 5. BMI = Diff. +0.6 kg/m^2 (p>0.05) not sig.	-	-	-	-
Ali M et al 2012[12]	1. HbA1C (%)= IG baseline 8.2 to 6.6 (change -1.6). CG baseline 8.1 to 7.5 (change -0.6). 2. RBG (mmol/L)= IG baseline 8.80 to 6.88 (change -1.92). CG baseline 9.53 to 9.04 (change -0.49). 3. SBP (mmHg)= IG baseline 146.26 to 126.17 (change -20.09). CG baseline 136.22 to 139.17 (change +2.95). 4. DBP (mmHg)= IG baseline 87.13 to 81.04 (change -6.09). CG baseline 85.65 to 81.7 (change -3.95). 5. TC (mmol/L)= IG baseline 4.15 to 4.12 (change -0.03). CG baseline 3.66 to 3.14 (change -0.52). 6. LDL (mmol/L)= IG baseline 2.35 to 1.97 (change -0.38). CG baseline 1.81 to 1.25 (change -0.56). 7. HDL (mmol/L)= IG baseline 1.19 to 1.46 (change +0.27). CG baseline 1.2 to 1.25 (change +0.05). 8. TG (mmol/L)= IG baseline 1.35 to 1.52 (change +0.17). CG baseline 1.44 to 1.78 (change +0.34). 9. BMI (kg/m^2)= IG baseline 30.84 to 26.98 (change -3.86). CG baseline 29.82 to 28.73 (change -1.09).	1. HbA1C= Diff. -1.0% (p< 0.001) sig. 2. RBG= Diff. -1.43 mmol/L (p< 0.001) sig. 3. SBP= Diff. -23.04 mmHg (p= 0.012) sig. 4. DBP= Diff. -2.14mmHg (p = 0.748) not sig. 5. TC= Diff. -0.49 mmol/L (p< 0.001) sig. 6. LDL= Diff. -0.18 mmol/L (p< 0.001) sig. 7. HDL= Diff. +0.22 mmol/L (p< 0.001) sig. 8. TG= Diff. +0.17 mmol/L (p= 0.404) not sig. 9. BMI= Diff. -2.77 kg/m^2 (p= 0.067) not sig.	1. QOL SF36 (score)= overall IG baseline 65.61 to 79.09 (change +13.48). CG baseline 70.04 to 66.53 (change -3.51). 2. DQOL (score)= overall IG baseline 29.81 to 23.48 (change -6.33). CG baseline 30.52 to 27.87 (change -2.65).	1. QOL SF36 (score)= Diff. +16.99 (p=0.001) sig. 2. DQOL (score)= Diff.-3.68 (p=0.119) not sig.	NA	NA
Jarab et.al 2012[13]	1. HbA1C (%)= IG baseline 8.5 to 7.7 (change -0.8). CG baseline 8.4 to 8.5 (change +0.1). 2. FBG (mmol/L)= IG baseline 12.5 to 10.2 (change -2.3). CG baseline 11.7 to 12.6 (change +0.9).	1. HbA1C= Diff. -0.9% (p=0.019) sig. 2. FBG= Diff. -3.2 mmol/L (p= 0.014) sig.	NA	NA	Medication non-adherence (%)= IG baseline 74.1 to 28.6 (reduce 45.5). CG baseline 70.9 to 64.6 (reduce 6.3).	Non-adherence= Diff. 39.2% (p= 0.003) sig.
Author, Year	**Therapeutic Effectiveness**		**Quality of Life**		**Drug Related Problems (DRP)**	
	Result	**Difference Between Groups**	**Result**	**Difference Between Groups**	**Result**	**Difference Between Groups**
Jarab et.al 2012[13]	3. SBP (mmHg)= IG baseline 132 to 126.2 (change -20.09). CG baseline 134 to 135.1	3. SBP= Diff. -21.19 mmHg (p= 0.035) sig.	-	-	-	-

(Cont.)	(change +1.1). 4. DBP (mmHg)= IG baseline 85 to 77.9 (change -7.1). CG baseline 85 to 86.8 (change +1.8). 5. TC (mmol/L)= IG baseline 4.7 to 4.0 (change -0.7). CG baseline 4.7 to 4.71 (change +0.1). 6. LDL (mmol/L)= IG baseline 2.1 to 1.5 (change -0.6). CG baseline 2.2 to 2.2 (no change). 7. HDL (mmol/L)= IG baseline 1.3 to 1.15 (change -0.15). CG baseline 1.3 to 1.3 (No change). 8. TG (mmol/L)= IG baseline 1.9 to 1.4 (change -0.5). CG baseline 2.0 to 2.2 (change +0.2). BMI (kg/m^2)= IG baseline 32.4 to 31.9 (change -0.5). CG baseline 32.8 to 33.2 (change +0.4).	4. DBP= Diff. -8.9 mmHg (p=0.026) not sig. 5. TC= Diff.-0.8 mmol/L (p= 0.040) sig. 6. LDL= Diff. -0.6 mmol/L (p=0.031) sig. 7. HDL= Diff. -0.15 mmol/L (p= 0.728) not sig. 8. TG= Diff.-0.7 mmol/L (p= 0.017) sig. BMI= Diff. -0.9 kg/m^2 (p= 0.189) not sig.				
Mourão et al. 2013[14]	1. HbA1C (%)= IG baseline 9.9 to 9.3 (change -0.6). CG baseline 9.5 to 10.2 (change +0.7). 2. FBG (mg/dL)= IG baseline 177.75 to 156.35 (change -21.4). CG baseline 174.4 to 187.8 (change +13.4). 3. SBP (mmHg)= IG baseline 152.9 to 140.8 (change -12.1). CG baseline 140.4 to 137.5 (change -2.9). 4. DBP (mmHg)= IG baseline 85.1 to 82.1 (change -3.0). CG baseline 82.9 to 80.4 (change -2.5). 5. TC (mg/dL)= IG baseline 216.3 to 189.3 (change -27). CG baseline 207.5 to 207.8 (change +0.3). 6. LDL (mg/dL)= IG baseline 128.9 to 105.9 (change -23). CG baseline 123.0 to 123.5 (change +0.5). 7. HDL (mg/dL)= IG baseline 51.8 to 53.5 (change +1.7). CG baseline 53.4 to 50.6 (change -2.8). 8. TG (mg/dL)= IG baseline 171.2 to 152.2 (change -19). CG baseline 162.4 to 177.4 (change +15).	1. HbA1C= Diff. -1.3% (p=0.001) sig. 2. FBG= Diff. -34.8 mg/dL (p= 0.007) sig. 3. SBP= Diff.-9.2 mmHg (p= 0.013) sig. 4. DBP= Diff. -0.5 mmHg (p=0.809) not sig. 5. TC= Diff. -27.3 mg/dL (p= 0.008) sig. 6. LDL= Diff. -23.5 mg/dL (p=0.026) sig 7. HDL= Diff. -4.5 mg/dL (p= 0.020) sig. 8. TG= Diff. -34 mg/dL (p= 0.007) sig.	NA	NA	1. Need additional drug therapy (%) = IG baseline 3.8 to 9.2 (change + 5.4), CG =NA 2. Unnecessary drug therapy (%)= IG baseline 21.2 to 7.7 (change -13.5), CG =NA 3. Ineffective drug (%)= IG baseline 30.8 to 45.6 (change +14.8), CG = NA 4. Dose to low (%)= IG baseline 22.7 to 21.8 (change -0.9), CG=NA 5. Dose too high (%)= IG baseline 1.2 to 2.8 (change +1.6), CG=NA 6. ADR (%)=IG baseline 6.5 to 1.2 (change -5.3), CG =NA 7. Non-compliance (%)= IG baseline 13.8 to 11.7 (change -2.1), CG =NA	Average DRP sig. reduce p< 0.001
Author, Year	**Therapeutic Effectiveness**		**Quality of Life**		**Drug Related Problems (DRP)**	
	Result	**Difference Between Groups**	**Result**	**Difference Between Groups**	**Result**	**Difference Between Groups**
Mourão et al. 2013[14] (Cont.)	9. BMI (kg/m^2)= IG baseline 30.3 to 30.4 (change +0.1). CG baseline 30.3 to 30.0 (change -0.3).	9. BMI= Diff. -0.2 kg/m2 (p= 0.106) not sig.	-	-	-	-

Lenander et.al 2014[15]	NA	NA	NA	NA	1. ADEs= IG baseline 0.64 to 0.52 (reduce 0.12). CG baseline 0.53 to 0.50 (reduce 0.03). 2. Wrong drug= IG baseline 0.32 to 0.31 (reduce 0.01). CG baseline 0.33 to 0.33 (no change). 3. Adherence= IG baseline 0.37 to 0.21 (reduce 0.16). CG baseline 0.21 to 0.11 (reduce 0.10). 4. Dose problem (too high/low)= IG baseline 0.17 to 0.12 (reduce 0.05). CG baseline 0.12 to 0.03 (reduce 0.09). 5. NAT= IG baseline 0.04 to 0.03 (reduce 0.01). CG baseline 0.05 to 0.00 (reduce 0.05). 6. UDT= IG baseline 0.01 to 0.00 (reduce 0.01). CG baseline 0.05 to 0.03 (reduce 0.02).	1. ADEs = not sig. (p> 0.05). 2. Wrong drug= not sig.(p> 0.05). 3. Adherence= Diff. 0.06 sig. (p=0.02). 4. Dose problem (too high/low)= not sig (p> 0.05). 5. NAT= not sig.(p> 0.05). 6. UDT= not sig (p> 0.05).
Chung et al. 2014[16]	1. HbA1C (%)= After intervention IG= -4.884, CG= -0.159. 2. FBG (mmol/L)= After intervention IG= -3.264, CG= -0.268.	1. HbA1c= Diff. -4.725% (p<0.001) sig. 2. FBG= Diff. 2.996 mmol/L (p=0.001) sig.	NA	NA	Adherence (%)= after intervention IG= 90, CG= 71.	Diff. 19% p=0.007 sig.
Kjeldsen et al. 2014[17]	1. BG= NR 2. SBP (mmHg)= IG basic -7.5, IG extended -6.7, CG -1.4.	1. BG= Not sig. 2. SBP (mmHg)= Diff -6.1 to basic, -5.3 to extended, p=0.033 sig.	HRQOL (Score)= overall IG basic 0.050, IG extended 0.060, CG 0.003.	Diff 0.047 to basic, 0.057 to extended, p=0.084 sig.	1. Disease knowledge (score)= IG basic 1.0, IG extended 1.8, CG -0.2. 2. Non-adherence (%)= IG basic 13.5, IG extended 22.5, CG 26.8.	1. Disease knowledge= Diff. 0.8 to basic, 2.0 to extended, p=0.016 sig. 2. Non adherence= Diff. 13.3 to basic, 4.3 to extended, p=0.246 not sig.