Medication management in patients with diabetes

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Pharmacist-led self-management interventions to improve diabetes outcomes

A systematic literature review and meta-analysis

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Chapter 03

ABSTRACT

Background. Treatment of diabetes requires a strict treatment scheme which demands patient self-management. Pharmacists are in a good position to provide self-management support. This review examines whether pharmacist-led interventions to support self-management in diabetes patients improve clinical and patient-reported outcomes.

Methods. This review was conducted according to the PRISMA guidelines. An extended literature search was conducted with the keywords "pharmacist", "diabetes" and "self-management" using the electronic databases Pubmed, Embase, CINAHL, PsycINFO, Web of Science and the Cochrane Library from the beginning of the database through September 2017. In addition, reference lists of systematic reviews and included studies were searched. Eligibility criteria included; self-management intervention tested with an RCT, performed in an ambulatory care setting, led by a pharmacist and reporting at least one clinical- or patient-reported outcome. Primary outcomes were HbA1c (– as this is a clinical parameter for long-term diabetes follow-up), self-management and components of intervention. Secondary outcomes were blood glucose, blood pressure, BMI, lipids, adherence to medication, quality of life and diabetes knowledge. For the meta-analysis HbA1c values were pooled with a random-effects model in Revman 5.3. Risk of bias was assessed with the Cochrane Risk of Bias tool.

Results. Twenty-four studies representing 3,610 patients were included. Pharmacist-led self-management interventions included education on diabetes complications, medication, lifestyle and teaching of self-management skills. Some studies focused on patient needs through a tailored intervention. No key components for a successful self-management intervention could be identified. Pharmacist-led self-management interventions improve HbA1c levels with a mean of 0.71% (CI -0.91, -0.51; overall effect $P < 0.0001$) and had a positive effect on blood pressure (SBP -5.20 mm Hg [-7.58; -2.92], DBP -3.51 mmHg [-6.00; -1.01]), BMI (-0.49 kg/m^2 [-0.79; -0.19]), lipids (total cholesterol -0.19 mmol/l [-0.33; -0.05], LDL-C mmol/l -0.16 [-0.26; -0.06], HDL-C 0.32 mmol/l [0.02; 0.61]), self-management skill development and adherence to medication.

Conclusion. Pharmacist-led self-management interventions significantly improve HbA1c values in diabetes patients. These results underline the added value of pharmacists in patient-related care. Pharmacists should offer self-management support to diabetes patients in order to improve diabetes outcomes.

INTRODUCTION

Diabetes is a disease which is complex to manage. Treatment consists of lifestyle adaptations often combined with medication to control blood glucose levels.[1] Despite available treatment, diabetes is often associated with complications and co-morbidities which increase the complexity of disease management even further.[2–4] Self-management is an essential part of diabetes disease management and is mainly the patient's responsibility. Self-management of chronic conditions has been defined as: "The individual's ability to manage the symptoms, treatment, physical and psychosocial consequences and lifestyle changes inherent in living with a chronic condition. Efficacious self-management encompasses the ability to monitor one's condition and to effect the cognitive, behavioral and emotional responses necessary to maintain a satisfactory quality of life.".[5,6] Patients – especially those with complex diseases – often need support in developing and maintaining self-management skills.[7]

Self-management interventions led by physicians, nurses, dieticians and diabetes educators have been shown to improve HbA1c values in diabetes patients.[8,9] Over the years, several reviews have shown that pharmacists also contribute additional value in diabetes care for patients. [10–13] Although, these reviews either studied any type of pharmacist intervention instead of only self-care related interventions [11–13] or merely focused on adherence [10]. For the U.S., meta-analyses for HbA1c changes were presented by Greer et al., 2016.[11] Machado et al., 2007 presented these figures for studies conducted worldwide.[12] But both studies did not focus on the interventions to improve self-management skills. Furthermore, the meta-analyses either were limited in their scope to only the U.S. or are rather outdated. A comprehensive updated review is needed to summarize the current evidence on the role of pharmacists in supporting self-management skills in diabetes patients. This is all the more important because of the still ongoing paradigm shift of the role of the pharmacist from being a drug supplier to a drug therapy manager.[14,15] The aim of this systematic review is to examine the effectiveness of pharmacist-led interventions to support self-management in order to improve clinical- and patient-reported diabetes outcomes.

METHODS

This review was reported according to the PRISMA statement.[16] The protocol was registered in the Prospero International Prospective Register of Systematic Reviews (registration number: CRD42016041859).

Research question

This review assessed the effect of pharmacist-led self-management interventions for diabetes patients on clinical- and patient reported outcomes in randomized controlled trials. Primary outcomes were HbA1c, self-management skills and intervention components. Secondary outcomes were blood glucose, blood pressure, BMI, lipids, adherence to medication, quality of life and diabetes knowledge.

Data Sources and Searches

Pubmed, Embase, Cinahl, PsycINFO, Web of Science and the Cochrane Library were searched from the start date of the database through to September 2017. Keywords used included 'pharmacist', 'diabetes' and 'self-management' (Appendix Table 1). Whenever possible MeSH terms and advanced search strategies were used (Appendix Figure 1). The electronic database searches were complemented by manually reviewing the references of relevant reviews and included studies.

Inclusion criteria

A study was included in the review if; (1) the study population was diagnosed with diabetes excluding gestational diabetes, (2) the intervention targeted patients' self-management[5,6] in an ambulatory care setting, (3) the pharmacist, or a member of the pharmacy team, was involved in the intervention, (4) data on one or more outcome measures were reported e.g. HbA1c, diabetes self-care activities, adherence, (5) the study design was a randomized controlled trial, (6) the full text article was published in either English or Dutch and (7) it was an original study published in a peer-reviewed journal.

Self-management interventions are not always described as such. Therefore, both direct and indirect self-management interventions were included. By indirect self-management interventions we mean interventions containing components that eventually could lead to improved self-management skills, e.g. diabetes and lifestyle education or concordant goal setting.

Study selection

Two reviewers, LvE and LvD, independently assessed all titles and abstracts identified with the initial searches. For all potentially eligible studies the full text papers were obtained via the University of Groningen catalogues, open sources and by emailing first authors. Full text papers were read by both reviewers (LvE and LvD) independently for final inclusion. Any disagreements between the reviewers were resolved by discussion or consultation with a third party (HdG or KT).

Data Extraction and Quality Assessment

The following data were extracted from the included studies: general study characteristics, description of the study population, follow-up time, number and duration of contact moments during intervention, description and components of the intervention (diabetes education, medication, lifestyle, individual care plan or goal setting, self-management skills, self-monitoring blood glucose (SMBG) and other, group or individual intervention, education for intervention team), clinical outcomes (HbA1c, blood glucose, blood pressure, BMI, lipid profile and other) and patient-reported outcomes (adherence, diabetes knowledge, quality of life, self-care/self-management and other) (Appendix Table 2). Also, it was noted whether interventions were tailored according to the patient's needs. A study was categorized as being tailored if the author made this statement in the research paper. The review team did not base the classification of tailoring on literature statements.[17,18] The study data were extracted by LvE and double checked for eight papers by LvD, KT and HdG. Any disagreements were discussed until consensus was reached.

The risk of bias in individual studies was assessed with the Cochrane Risk of Bias tool by LvE.[19] This assessment was double checked by LvD, KT and HdG by assessing the risk of bias in eight studies. Any disagreements were discussed until consensus was reached.

Data Synthesis and Analysis

Interventions across the included studies were analyzed and described narratively.

Outcomes were divided into clinical outcomes (HbA1c, glucose levels, blood pressure, BMI, lipids and other) and patient-reported outcomes (adherence, diabetes knowledge, quality of life, self-care and other). Results for HbA1c, blood glucose, blood pressure, BMI, lipids and Summary of Diabetes Self-care Activities Assessment (SDSCA) were pooled in a meta-analysis. Meta-analyses were performed with Review Manager 5.3 by using a random effects model because of clinical heterogeneity across the included studies. Subgroup analyses were performed for the outcome HbA1c, for different intervention elements (follow-up time, baseline HbA1c ≤ 7% and education for intervention team) in order to explain any heterogeneity (I^2) across the studies and to explore key intervention components. Sensitivity analyses were performed to test for robustness of the results regarding including studies with a cluster randomization design and studies with a high risk of bias affecting the outcome HbA1c. Results for adherence, diabetes knowledge and quality of life were described narratively.

RESULTS

In total 5,919 hits were identified from the electronic database searches, of which 3,996 were unique. After the title and abstract assessment 3,932 references were excluded because they did not meet the inclusion criteria. The full text of 64 papers was assessed, with 24 papers finally being included in the review. (Figure 1, Appendix Table 3 for extended data extraction information). Reasons for exclusion after full-text assessment are presented in Appendix Table 4. Study characteristics of the included studies are presented in Table 1 and characteristics of the study populations of the included studies are presented in Table 2.

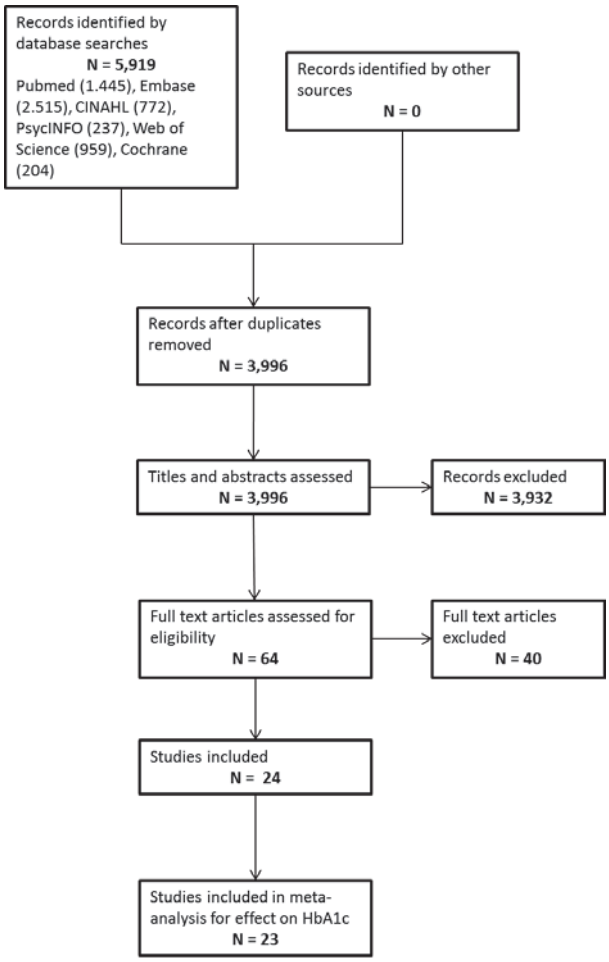

Figure 1: Flow chart study selection

Table 1: Main study characteristics included studies.

			Intervention topics							Outcomes											
										Clinical						Patient reported					
Author, year, country, study design	Follow-up time (in months)	Number of contact moments (time)	Diabetes education	Medication	Lifestyle	Individual care plan/ goal setting	Self-management skills	SMBG	Other	HbA1c	Glucose-levels	Blood pressure	BMI	Lipid profile	Other	Adherence	Diabetes knowledge	QoL	Self-care/ self-management	Other
Armour 2004[20], Australia, cluster RCT	9	at least 4 visits (NR)		X	X	X	X	X	X	X								X		X
Butt 2015[23], Malaysia, parallel RCT	6	3 visits (in total 55-75 min.)	X	X	X			X	X	X	X		X	X		X	X	X		
Cani 2015[24], Brazil, parallel RCT	6	6 visits (NR)	X	X	X			X	X	X						X		X		X
Choe 2005[25], U.S., parallel RCT	12-24	12 visits/ telephone calls (first visit 60 min.)		X			X		X	X					X					
Cohen 2011[43], U.S., parallel RCT	6	4 weekly visits (120 min.) + 5 monthly visits (90 min.)	X	X	X	X	X	X	X	X		X		X				X	X	X
Doucette 2009[26], U.S., parallel RCT	12	4 visits (NR)		X		X	X		X	X		X		X					X	
Farsaei 2011[27], Iran, parallel RCT	3	2 education sessions followed by weekly phone calls (NR)		X	X	X	X		X	X	X									
Jacobs 2012[28], U.S., parallel RCT	12	at least 3 visits (NR)	X	X	X	X	X		X	X		X		X						
Jahangard-Rafsanjani 2015[29], Iran, parallel RCT	5	5 visits (30 min.)	X		X	X	X	X	X	X		X	X			X			X	X
Jameson 2010[30], U.S., parallel RCT	12	On average 6 visits (30-60 min.) + 3 telephone calls (10-20 min.)		X	X		X	X		X										X

Table 1: Continued.

			Intervention topics							Outcomes										
										Clinical						Patient reported				
Author, year, country, study design	Follow-up time (in months)	Number of contact moments (time)	Diabetes education	Medication	Lifestyle	Individual care plan/ goal setting	Self-management skills	SMBG	Other	HbA1c	Glucose-levels	Blood pressure	BMI	Lipid profile	Other	Adherence	Diabetes knowledge	QoL	Self-care/ self-management	Other
Jarab 2012[31], Jordan, parallel RCT	6	1 visit (NR) + 8 telephone calls (20 min.)	X	X	X			X	X	X	X	X	X	X		X			X	
Kjeldsen 2015[32], Denmark, parallel RCT	6	at least 4 visits (in total 65-130 min.)		X		X			X			X				X	X	X	X	X
Korcegez 2017[33], Cyprus, parallel RCT	12	5 visits (NR)	X	X	X	X	X	X	X	X	X	X	X	X		X			X	
Kraemer 2012[34], U.S., parallel RCT	12	On average 5.4 [4.6; 6.3] visits (NR)				X	X	X		X	X	X		X		X	X		X	
Krass 2007[21], Australia, cluster RCT	6	5 visits (NR)	X	X	X	X	X	X	X	X		X	X	X				X		
Mehuys 2011[22], Belgium, cluster RCT	6	visit at start and at each prescription-refill visit (NR)	X	X	X					X	X					X	X		X	
Nascimento 2015[35], Portugal, parallel RCT	6	at least 2 visits (NR)		X			X			X	X					X			X	
Odegard 2005[36], U.S., parallel RCT	12	On average 2.1 ± 1.0 visits (30 min.) + 4.5 ± 1.9 telephone calls (10 min.)		X	X	X	X	X	X	X						X				X
Samtia 2013[37], Pakistan, parallel RCT	5	at least 2 visits (NR)	X	X	X		X	X	X	X	X		X			X	X			X
Sarkadi 2004[38], Sweden, parallel RCT	12-24	12 visits (NR)	X	X	X		X	X	X	X										X

Table 1: Continued.

			Intervention topics							Outcomes										
										Clinical						Patient reported				
Author, year, country, study design	Follow-up time (in months)	Number of contact moments (time)	Diabetes education	Medication	Lifestyle	Individual care plan/ goal setting	Self-management skills	SMBG	Other	HbA1c	Glucose-levels	Blood pressure	BMI	Lipid profile	Other	Adherence	Diabetes knowledge	QoL	Self-care/ self-management	Other
Shao 2017[39], China, parallel RCT	6	2 education sessions (NR), 3 face-to-face interviews (NR), 6 telephone interviews (NR)	X	X	X		X	X		X	X	X	X	X		X				
Taveira 2010[41], U.S., parallel RCT	4	4 weekly group visits (120 min.)	X		X	X	X			X		X	X	X					X	X
Taveira 2011[40], U.S., parallel RCT	6	4 weekly visits (120 min.) + 4 monthly visits (NR)	X	X	X	X	X	X		X		X		X					X	X
Wishah 2015[42], Jordan, parallel RCT	6	3 visits (30 min.)	X	X	X	X	X		X	X	X		X	X		X	X		X	

Table 2: Main characteristics of the study populations.

Study		N	Sex (% male)	Age (yrs) (mean, SD)	Baseline HbA1c (% , SD)	Insulin users (%)	DM Type	Comorbidities
Armour 2004[20]	IG	53	45	64 ±9	7.9 ±1.5	NR	2	Heart disease, hypertension, hyperlipidemia
	CG	46	51	65 ±10	7.4 ±1.2	NR		
Butt 2015[23]	IG	33	39.4	57.4 ±7.2	9.66 ±1.57	62.5	2	NR
	CG	33	42.4	57.1 ±10.8	9.64 ±1.41	46.3		
Cani 2015[24]	IG	34	38.2	61.9 ±9.6	9.78 ±1.55	100	2	NR
	CG	36	38.9	61.6 ±8.1	9.61 ±1.38	100		
Choe 2005[25]	IG	41	48.8	52.2 ±11.2	10.1 ±1.8	29.3	2	NR
	CG	39	46.1	51.0 ±9.0	10.2 ±1.7	30.8		
Cohen 2011[43]	IG	50	100	69.8 ±10.7	7.8 ±1.0	NR	2	Heart failure, stroke, coronary heart disease, COPD, mood disorder
	CG	49	96	67.2 ±9.4	8.1 ±1.4	NR		
Doucette 2009[26]	IG	31	41.7	58.7 ±13.3	7.99 ±1.45	NR	2	NR
	CG	35	47.6	61.2 ±10.9	7.91 ±1.91	NR		
Farsaei 2011[27]	IG	87	36.8	53.4 ±9.8	9.3 ±1.7	13.1	2	Hypertension, dyslipidemia, heart disease, thyroid disease, renal disease
	CG	87	31.8	52.9 ±8.5	8.9 ±1.1	11.5		
Jacobs 2012[28]	IG	72	68	62.7 ±10.8	9.5 ±1.1	19	2	Retinopathy, nephropathy, neuropathy
	CG	92	55	63.0 ±11.2	9.2 ±1.0	15		
Jahangard-Rafsanjani 2015[29]	IG	45	51	57.3 ±8.6	7.6 ±1.6	NR	2	NR
	CG	40	48	55.9 ±8.7	7.51 ±1.8	NR		
Jameson 2010[30]	IG	52	48.9	49.3 ±10.8	10.4 ±1.2	23	NR	NR
	CG	51	49	49.7 ±10.9	11.1 ±1.6	28		

Table 2: Continued.

Study		N	Sex (% male)	Age (yrs) (mean, SD)	Baseline HbA1c (% , SD)	Insulin users (%)	DM Type	Comorbidities
Jarab 2012[31]	IG	77	57.6	63.4 ±10.1	8.5	65.9	2	NR
	CG	79	55.8	65.3 ±9.2	8.4	69.8		
Kjeldsen 2015[32]	IG-B	33	57.9	63 ±8.8	NR	NR	2	NR
	IG-E	37	59.5	63.4 ±7.8	NR	NR		
	CG	102	62.4	62.1 ±10.2	NR	NR		
Korcegez 2017[33]	IG	75	22.7	61.8 ±10.38	8.29 ±0.89	54.7	2	Hypertension, dyslipidemia, thyroid disease, rheumatoid arthritis, asthma, heart failure, osteoporosis, psychological disorders
	CG	77	26.0	62.2 ±9.54	8.31 ±0.84	51.9		
Kraemer 2012[34]	IG	36	61.1	55.6 ±6.8	7.28	13.9	1 & 2	NR
	CG	29	38.7	52.6 ±9.2	7.38	32.3		
Krass 2007[21]	IG	125	51	62 ±11	8.9 ±1.4	NR	2	Hypertension, hyperlipidemia
	CG	107	51	62 ±11	8.3 ±1.3	NR		
Mehuys 2011[22]	IG	153	51.0	63	7.7	6.8	2	NR
	CG	135	53.7	62.3	7.3	11.4		
Nascimento 2015[35]	IG	44	56.8	74.2 ±5.4	8.6 ±1.2	27.3	2	Hypertension, dyslipidemia, vascular complications
	CG	43	58.1	72.3 ±4.5	8.2 ±0.7	34.9		
Odegard 2005[36]	IG	39	52	51.6 ±11.6	10.2 ±0.8	26	2	NR
	CG	27	64	51.9 ±10.4	10.6 ±1.4	38		
Samtia 2013[37]	IG	108	52.8	46.1	8.51	8.3	2	NR
	CG	97	48.2	42.3	8.54	14.1		
Sarkadi 2004[38]	IG	33	NR	66.4	6.45	NR	2	NR
	CG	31	NR	66.5	6.45	NR		

Table 2: Continued.

Study		N	Sex (% male)	Age (yrs) (mean, SD)	Baseline HbA1c (% , SD)	Insulin users (%)	DM Type	Comorbidities
Shao 2017[39]	IG	99	51.0	58.7 ±10.59	7.38 ±1.71	NR	2	NR
	CG	100	47.5	59.2 ±10.34	7.37 ±1.44	NR		
Taveira 2010[41]	IG	58	91.4	62.2 ±10.3	8.5 ±1.5	NR	2	Hypertension, hyperlipidemia, coronary artery disease, congestive heart failure, COPD
	CG	51	100	66.8 ±10.2	7.9 ±1.1	NR		
Taveira 2011[40]	IG	44	100	60.2 ±9.3	8.3 ±1.7	NR	2	Depression, coronary artery disease, anxiety, schizophrenia, bipolar, PTSD
	CG	44	95.5	61.4 ±9.9	8.5 ±1.9	NR		
Wishah 2015[42]	IG	52	38.5	52.9 ±9.6	8.9 ±1.6	NR	2	NR
	CG	54	48.1	53.2 ±11.2	8.2 ±1.3	NR		

Description of included studies

Three of the included studies had a cluster randomized design [20–22] and twenty-one were randomized controlled trials [23,24,33–42,25–32] (Table 1). All studies were published from 2004 onwards. Most of the studies were conducted in North America (9) [25,26,28,30,34,36,40,41,43], followed by Asia (7) [23,27,29,31,37,39,42], Europe (5) [22,32,33,35,38], Australia (2) [20,21] and South America (1) [24]. The majority of the studies focused primarily on diabetes mellitus type 2 patients (22) [20,21,31–33,35–41,22,42,43,23–29], one study included both type 1 and type 2 patients [34] and one study did not specify the type of diabetes [30]. In total the included studies represented 3,610 participants with a mean age ranging from 44 to 73 years of age. The median follow-up time was 6 months [21,22,43,23,24,31–33,35,40,42], four studies had a follow-up time of less than six months [27,29,37,41] and ten of more than six months [20,25,26,28,30,34,36,38,39].

Description of intervention

The interventions in the included studies were all provided by a trained pharmacist, either by the pharmacist alone [20,21,30–34,36,37,39,42,22–29] or within a multi-disciplinary team [38,40,41,43]. One study did not specify the intervention team, besides including a pharmacist [35]. Most interventions targeted the individual patient [20,21,31–34,36,37,39,42,22–26,28–30] whereas some interventions used group sessions [38,40,41,43]. One study did not specify whether the intervention was offered in an individual or group setting [27]. Fifteen studies reported offering a tailored intervention based on a patient's specific needs [20,21,35,36,40–42,24,27,29–34].

The interventions in the included studies varied in the intensity as well as the number and type of components. The intensity, measured as the frequency of contact moments, differed across the studies from once a week to once every three months. Face-to-face contact with the pharmacists (18) [20,21,34,35,37,38,40–43,22–24,26,28,29,32,33] as well as a combination of face-to-face contacts and telephone contact with the pharmacists (6) [25,27,30,31,36,39] were reported in the studies. The total contact time varied across the studies, though not all studies reported this information (Table 1) [20,22,39,40,24,26–28,33,35,37,38]. Fifteen studies included diabetes education [21,22,39–43,23,24,28,29,31,33,37,38] either about diabetes in general or about acute and chronic complications. Education on medication was provided in twenty-one studies [20,21,31–33,35–40,42,22,43,23–28,30] and included education about adherence, dosage, drug-related problems, indication, storage and use. In nineteen studies education on lifestyle, including diet, exercise, foot care, and/or smoking cessation were part of the intervention [20,21,33,36–43,22–24,27–31]. In nineteen studies the intervention included self-management skills support [20,21,35–43,25–30,33,34] and in fifteen studies participants were trained in self-monitoring blood glucose [20,21,37–40,43,23,24,29–31,33,34,36]. A total of fourteen studies used either an individual care plan or goal setting to improve diabetes outcomes [20,21,40–43,26–

29,32–34,36]. Other less common interventions were the use of a diabetes diary [23,27,29], medication reviews by a pharmacist [20,21,25,26,28,33], and providing participants with written information [24,29,31,33,35,38,42].

Many different outcome measures were reported by the included studies (Table 1). They were divided in clinical and patient-reported outcomes.

Clinical outcomes

All studies reported HbA1c as an outcome measurement for their intervention. A meta-analysis was performed, with one study excluded because of an insufficient number of participants reporting HbA1c at the final follow-up [32].

The meta-analysis (Figure 2) shows an overall significant effect in favor of the intervention on HbA1c, with HbA1c levels improving by a mean of 0.71% (CI -0.91, -0.51; overall effect P < 0.0001). Several subgroup analyses were performed based on different study characteristics (Table 3, Appendix Figures 2A-I). None of these subgroup analyses showed a significant difference between groups.

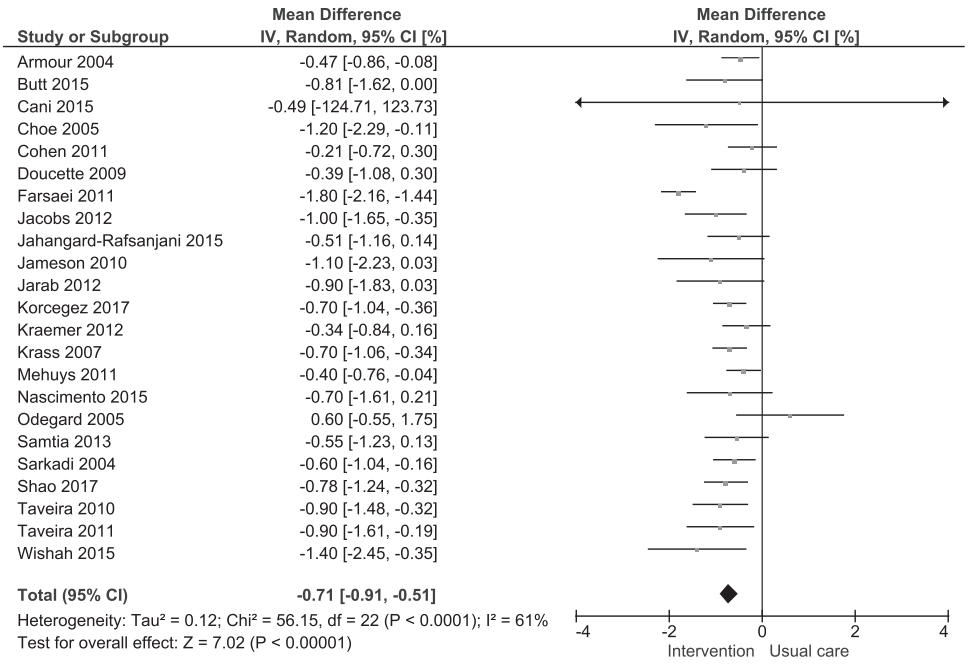

Figure 2: Meta-analysis HbA1c

Table 3: Subgroup analyses HbA1c

	Subgroup	N	I^2 (P-value)	CI	Test for subgroup differences
1	Overall	23	61% (P < 0.0001)	-0.71 [-0.91; -0.51]	-
2.1	Tailored intervention				P = 0.33, I^2 = 0%
2.1.1	Yes	13	72% (P < 0.0001)	-0.79 [-1.14; -0.44]	
2.1.2	No	10	0% (P = 0.58)	-0.60 [-0.76; -0.44]	
3.1	Group vs. individual intervention				P = 0.53; I^2 = 0%
3.1.1	Group	4	23% (P = 0.27)	-0.61 [-0.92; -0.30]	
3.1.2	Individual	19	65% (P < 0.0001)	-0.73 [-0.97; -0.50]	
4.1	Follow-up time				P = 0.57; I^2 = 0%
4.1.1	< 6 months	4	84% (P = 0.0002)	-0.98 [-1.68; -0.28]	
4.1.2	6 months	10	0% (P = 0.55)	-0.62 [-0.80; -0.44]	
4.1.3	> 6 months	9	17% (P = 0.29)	-0.58 [-0.79; -0.37]	
5.1	Follow-up time				P = 0.30; I^2 = 5.0%
5.1.1	< 6 months	4	84% (P = 0.0002)	-0.98 [-1.68; -0.28]	
5.1.2	≥ 6 months	19	0% (P = 0.48)	-0.60 [-0.73; -0.48]	
6.1	HbA1c baseline cut off 7%				P = 0.21; I^2 = 37.7%
6.1.1	< 7%	2	0% (P = 0.45)	-0.49 [-0.82; -0.15]	
6.1.2	> 7%	21	62% (P < 0.0001)	-0.74[-0.96; -0.52]	
7.1	Education intervention team				P = 0.05; I^2 = 75%
7.1.1	Yes	7	0% (P = 0.90)	-0.51 [-0.68; -0.34]	
7.1.2	No	16	64% (P = 0.0003)	-0.85 [-1.14; -0.56]	
8.1	Adherence				P = 0.35; I^2 = 0%
8.1.1	Yes	12	76% (P < 0.00001)	-0.77 [-1.09; -0.46]	
8.1.2	No	11	0% (P = 0.63)	-0.60 [-0.79; -0.40]	
9.1	DRP/ side effects				P = 0.26; I^2 = 20.1%
9.1.1	Yes	9	79% (P < 0.00001)	-0.84 [-1.24; -0.41]	
9.1.2	No	14	0% (P = 0.68)	-0.57 [-0.73; -0.41]	
10.1	Individual Care Plan/ Goal setting				P = 0.42; I^2 = 0%
10.1.1	Yes	11	77% (P < 0.00001)	-0.76 [-1.11; -0.40]	
10.1.2	No	12	0% (P = 0.67)	-0.60 [-0.77; -0.42]	

Other clinical outcomes reported were blood glucose levels, blood pressure, BMI, and lipid profile (Table 4, Appendix Figures 3-6). Meta-analyses showed no significant reduction for blood glucose levels, but a significant improvement in systolic- and diastolic blood pressure (-5.20 mm Hg [-7.58; -2.92] and -3.51 mm Hg [-6.00; -1.01], respectively), BMI scores (-0.49 kg/m^2 [-0.79; -0.19]), total cholesterol levels (-0.19 mmol/l [-0.33; -0.05], LDL-C levels (-0.16 mmol/l [-0.26; -0.06] and HDL-C levels (0.32 mmol/l [0.02; 0.61].

Table 4: Pooled outcomes clinical parameters

Outcome	Pooled results (mean, CI)
Blood glucose (mmol/l) [22,23,27,31,33–35,37,39,42]	-0.26 [-0.97; 0.46]
Blood pressure (mm Hg)	
Systolic blood pressure [21,26,43,28,29,31,33,34,39–41]	-5.20 [-7.48; -2.92]
Diastolic blood pressure [21,26,28,29,31,33,34,39,41]	-3.51 [-6.00; -1.01]
BMI (kg/m^2) [23,29,31,33,37,39,41,42]	-0.49 [-0.79; -0.19]
Lipids (mmol/l)	
Total cholesterol [21,23,31,33,34,39,42]	-0.19 [-0.33; -0.05]
LDL-C [23,26,43,28,31,33,34,39–42]	-0.16 [-0.26; -0.06]
HDL-C [23,31,33,34,39,42]	0.32 [0.02; 0.61]
Triglycerides [21,23,31,33,34,39,42]	-0.01 [-0.06; 0.03]

Patient reported outcomes

Self-management

Adherence to diabetes self-care was assessed in twelve studies [22,26,42,43,29,31–35,40,41]. Nine of them used the validated Summary of Diabetes Self-Care Activities assessment (SDSCA) [22,26,29,31,33,35,40,42,43]. This questionnaire consists of five domains (general diet, specific diet, exercise, self-monitoring blood glucose, foot care), and domain scores as well as an overall score can be calculated. Six studies reported domain scores [22,29,31,35,42,43]. The results of these six studies were pooled in a meta-analysis and a significant effect of pharmacist-led interventions was found for general diet, self-monitoring blood glucose, foot care and exercise (Figure 3A-F).

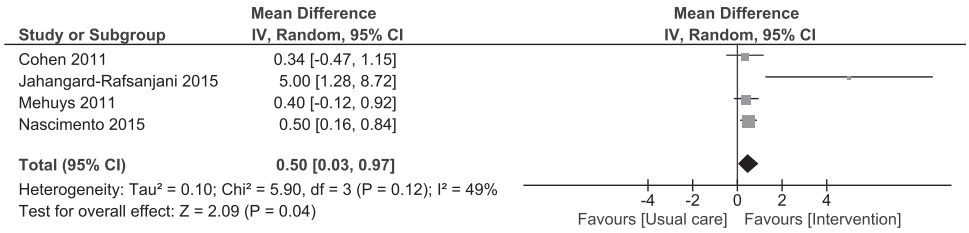

Figure 3A: Pooled results SDSCA General diet

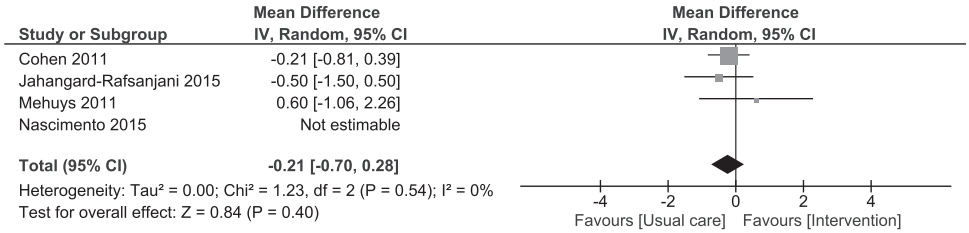

Figure 3B: Pooled results SDSCA Specific diet

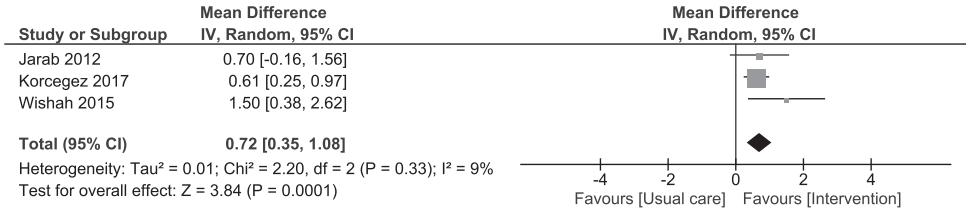

Figure 3C: Pooled results SDSCA Total diet

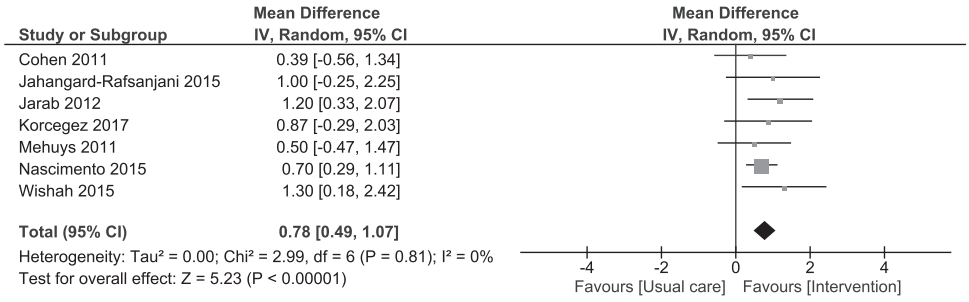

Figure 3D: Pooled results SDSCA Exercise

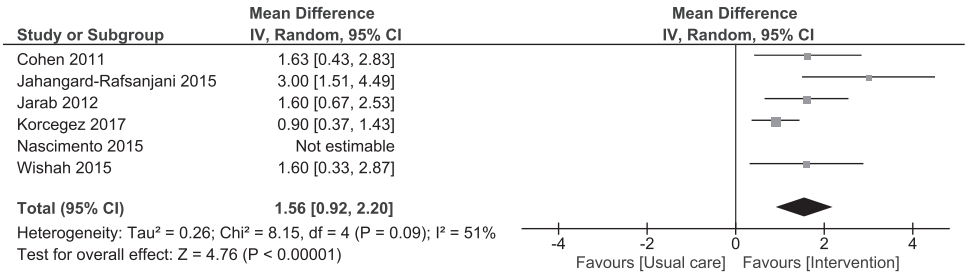

Figure 3E: Pooled results SDSCA SMBG

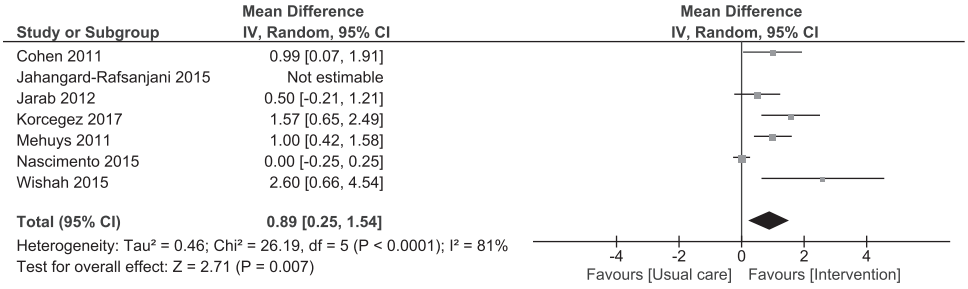

Figure 3F: Pooled results SDSCA Foot care

Adherence to medication

Adherence to medication was measured in thirteen studies [22,23,37,39,42,24,29,31–36]. Seven studies [23,24,29,31,33,39,42] used the validated Morisky-Green questionnaire. Due to different reporting strategies it was not possible to pool the results. Six studies reported significant improvement in adherence in the intervention group compared to the control group and one study reported improved adherence outcomes within the intervention group but did not compare intervention and control group [33].

Quality of life

Six studies [20,21,23,24,32,43] reported quality of life outcomes, of which three studies [21,23,32] used the validated EQ-5D(-3L) questionnaire. Due to the use of different versions of the questionnaire and differences in reporting strategies it was not possible to pool the results. Two studies reported significantly improved quality of life based on the results from the EQ-5D tool [21,23].

Diabetes knowledge

Diabetes knowledge was reported in six studies [22,23,32,34,37,42], of which three studies [22,34,42] used the validated Diabetes Knowledge Test of The Michigan Diabetes Research and Training Center. Due to the use of different reporting strategies it was not possible to pool the results. Only Wishah et al. 2015 reported significant improvement of diabetes knowledge [42].

Risk of bias

The risk of bias within studies was assessed with the Cochrane Risk of Bias tool. All but two [31,40] studies were subjected to some form of bias either at high risk or at an unclear risk due to lack of information (Appendix Figure 7). In total, eight studies were considered to have a low risk of bias [23,24,28,30,31,38,40,42].

Publication bias

The funnel plot for the pooled results of HbA1c can be considered symmetric and indicates that it is unlikely publication bias has been introduced in the analysis (Appendix Figure 8).

Sensitivity analysis

Two sensitivity analyses were performed. In the first sensitivity analysis the studies with a cluster randomization design were excluded, because none of these studies corrected for the clustering effect. The clustering effect is known for potential overestimation of the effect of the intervention. [44] After excluding these studies the weighted mean difference of HbA1c for the patient-level randomized studies was -0.76% [-1.00; -0.52]. This difference is of the same magnitude as the difference observed when including all studies.

The second sensitivity analysis was performed using only the eight studies with a relatively low risk of bias from influences on HbA1c. The weighted mean difference of HbA1c for studies with a low risk of bias was -0.84% [-1.11; -0.57]. This difference is also of the same magnitude as the difference observed when including all studies.

DISCUSSION

Summary of main findings

This review found evidence that pharmacist-led self-management interventions are beneficial for diabetes patients. All of the included studies used proxies to measure the effect of self-management interventions; only a minority directly measured the effect of self-management

interventions on self-management skills. Overall, pharmacist-led interventions had a positive effect on HbA1c values, blood pressure, BMI and self-management skills as shown by the results of the meta-analyses. Also, the results suggest pharmacist-led self-management interventions improve adherence to medication, diabetes knowledge and quality of life.

The results on HbA1c values in the meta-analysis showed a significant effect of pharmacist-led interventions. The magnitude of this reduction (-0.71% [-0.91; -0.51]) can be considered as clinically relevant and can be associated with risk reduction in microvascular complications.[45] These findings are in agreement with the findings of Machado et al. 2007, who reported a pooled effect of -1.00% ± 0.28% on HbA1c values. However, in their review all kinds of pharmacist interventions for diabetes patients were included.[12] Compared to systematic reviews on the effect of self-management interventions by either a physician, nurse or diabetes educator, the effect of pharmacist-led self-management interventions was over three times larger.[9] The added value of pharmacist-led interventions for diabetes goal attainment is supported by the findings of Greer et al., 2016, who reported a relative risk (1.83 [1.44; 2.33]) in favor of diabetes patients receiving pharmacist-led disease management.[11] The diversity of intervention contents in the included studies is also highlighted in previous reviews.[11–13]

Strengths and limitations

This study has several strengths. All of the studies included measured HbA1c values, which made it possible to compare the effect of the described interventions in a meta-analysis. Also, the results for blood glucose, blood pressure, BMI, lipids and self-management skills could be pooled in meta-analyses.

Though most studies used proxies to measure the effect of pharmacist-led self-management interventions, a few studies directly measured self-management. The results of these studies reveal a positive direct relation between the self-management intervention and the development of self-management skills in diabetes patients. This is most likely because the interventions in almost all of the included studies addressed medication and medication-related problems that are rather common among diabetes patients.[46,47]

This study also has some limitations. The reporting of the interventions and study results were very limited in some of the studies.[20,21,36,37,41,43,22,25–27,29,32,34,35] This made the risk of bias assessment difficult. However, the sensitivity analysis showed that excluding studies with a high risk of bias did not materially change the results of the meta-analysis of the HbA1c values.

The most frequently used instrument to measure self-management in diabetes patients was the SDSCA questionnaire. However, the SDSCA questionnaire pays limited attention to medication related issues.[48] Therefore, this questionnaire may not be the best instrument to measure the

effects of pharmacist-led and medication-related self-management support. A more suitable instruments for instance might be the MUSE questionnaire (Medication Understanding and Use Self-Efficacy Scale), which focuses on medication use and knowledge.[49] This scale can be used among patients with any level of health literacy.

The interventions reported in all of the included studies can be considered as complex interventions, because all of them consisted of multiple components. Also, the mechanisms of action for implicating practice were complex as this depends on both the pharmacists delivering and implementing the intervention and the patient implementing it into daily life. [50] In this review we have shown that these complex interventions have a positive influence on various diabetes related outcomes. Subgroup analyses did not provide evidence which of the components were essential for the effect. More sophisticated analyses, such as meta-regression analyses or modelling, could have given more insight into key components.[51] However, this was not possible due to the limited number of studies, data available and the different ways in which the data was presented in the included studies. Although, we have described the different components of pharmacist-led self-management interventions, the ideal composition of intervention components is still a black box.

Clinical implications and future research

The overall results of our study argue that pharmacists take an active role in improving patient diabetes self-management since the effectiveness of pharmacist-led interventions is at least comparable to that of other healthcare providers.[9] Although we were unable to identify specific factors contributing to the success of pharmacist-led self-management interventions, a tailored approach seems to be preferable for future developments.[52–54] In line with findings of previous studies; self-management needs depend on personal characteristics and development [55] and self-management support should focus on how to identify problems and how to take appropriate actions [7]. Another important factor for successful interventions might be the intensity of contact moments over time, with the intensity of contact moments appearing more important than the length of the intervention. This is demonstrated by Krass et al., 2011 and Odegard et al., 2005 who found that prolonging the follow-up time without sustaining the contact frequency did not further improve HbA1c values.[36,56] Moreover, some patient groups are more vulnerable to having low self-management skills than others. For example, patients with a low level of health literacy may benefit much more from self-management support compared to more health literate diabetes patients.[57,58] Summarizing the evidence, pharmacists should offer self-management support to diabetes patients in order to improve clinical- and patient reported diabetes outcomes.

Future research into self-management support should focus on developing an intervention from a multidisciplinary perspective to combine the knowledge from the different disciplines involved in

diabetes care. Most studies only focus on the role of a single healthcare professional. Combining the strengths of different disciplines might increase the effect of the intervention. Particular emphasis should be placed on vulnerable patient groups and using valid measurements of self-management skills in multiple dimensions.

CONCLUSION

This review demonstrates that pharmacists contribute additional value in self-management support interventions for diabetes patients. Pharmacists are involved in a variety of self-management interventions, which vary in many key aspects such as follow-up time and use of a tailored approach. Overall pharmacist-led self-management interventions have a positive effect on lowering HbA1c values.

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APPENDIX

Appendix Table 1: Keyword Search Terms

	Term	Text words
1	Pharmacist	Pharmacist, pharmacists, pharmacy, pharmacies, pharmaceutical
2	Diabetes	Diabetes, DM, diabetic
3	Self-management	Self-management, self management, self care, self-care, self efficacy, self-efficacy, patient participation, medication management, adherence, nonadherence, compliance, noncompliance

Appendix Table 2: Data Extraction Categories

Category	Information
General	First author, year of publication, country study was conducted, study design (parallel RCT or cluster RCT)
Study characteristics	Study setting, study design, follow-up period, sample size
Study population	Sex, age, baseline HbA1c, comorbidities
Intervention	Description of intervention, frequency of meetings, duration of meetings, intervention team, education for the intervention team. Intervention topics; diabetes education (complications, disease in general), medication (adherence, dosage, drug related problems, indication, insulin technique, side effects, storage, use), lifestyle (diet, exercise, eye examination, foot care, lifestyle, smoking cessation), individual care plan/goal setting, self-management skills, self-monitoring blood glucose and other (diabetes diary, discuss health beliefs, general health, identify problems, medical checks, medication review, monitor blood glucose by pharmacist, physical assessment, rationalize therapy, written information).
Outcomes	Clinical outcomes; glucose control (HbA1c, blood glucose), blood pressure (systolic blood pressure, diastolic blood pressure), body measures (BMI, height, weight, waist circumference), lipids (LDL, HDL, triglycerides, total cholesterol), other (dilated retinal examination, eGFR, test for diabetes neuropathy, urine microalbumine screening) Patient reported outcomes; adherence, diabetes knowledge, quality of life, self-care/self-management, other (BMQ, cardiovascular risk, death, depressive symptoms, glucose monitoring technique, hospital admissions, number of interventions delivered, medication knowledge, patient health questions, patient perceived competence, personal perception of diabetes, number of pharmacy visits, number of physician visits, tobacco use)

Appendix Table 3: Extended data extraction included studies.

Author	**Armour [1]**		
Year	2004		
Country	Australia		
Objective	To develop, implement, and evaluate a disease management service model for type 2 diabetes in community pharmacy.		
Study setting	Outpatient diabetes clinic		
Study design	Cluster randomized controlled trial		
Follow-up period	9 months		
Sample	N	239	
		Intervention	Control
	Sex (% male)	45	51
	Age (years ± SD)	64 ± 9	65 ± 10
	Baseline HbA1c (% ± SD)	7.9 ± 1.5	7.4 ± 1.2
	Comorbidities	Heart disease, hypertension, hyperlipidemia	
Intervention			
Description	All pharmacists conducted a medication review and monitored blood glucose levels of patients. Discretionary interventions included discussion of patient's health beliefs, providing adherence support, rationalizing therapy for patients, discussing potential or actual adverse drug effects, assessing lifestyle changes, and prompting for medical checks for complications. Visit 1 (recruitment) instructions for blood glucose monitoring, baseline data on diabetes history, quality of life (QoL), well-being, adherence. Visit 2; blood glucose readings, interventions based on identified issues, goals for next visit. Visit 3; blood glucose data, questions regarding lifestyle and self-care, suggestions for change, goal setting. Patients with medication related issues were given a full medication review. Subsequent visits to the pharmacy were tailored to individual needs.		
Frequency of meetings	At least 4 meetings		
Duration of meetings	Not reported		
Intervention team	Pharmacist		
Education intervention team	Yes, education manual and two-day workshop		
Intervention topics	Medication, lifestyle, individual care plan/goal setting, self-management skills, self-monitoring blood glucose, other		
Control group			
Description	Usual care. Data was collected at baseline and after 9 months. No blood glucose monitoring as this was considered to be an intervention.		
Outcomes			
Clinical outcomes	HbA1c, mean blood glucose		
Patient reported outcomes	QoL (ADDQoL), well-being (WB-Q12), risk of nonadherence (BMQ)		
Results			
Clinical results	HbA1c: Statistic significant reduction in intervention group (baseline; 7.9 ± 1.4, 9 months; 7.4 ± 1.3). No change in control group (7.4 ± 1.1). No significant difference between intervention and control group after 9 months. Blood glucose: Overall significant downward linear trend from visit 1 through 6.		
Patient reported results	QoL: No statistical significant changes. Well-being: WB-Q12 scores statistical significant increase in intervention group (baseline: 21.9 ± 6.8, 9 months 23.4 ± 6.8) no change in controls (baseline: 21.2 ± 7.3, 9 months 21.2 ± 6.6). Adherence: Statistical significant reduction of nonadherence in intervention group (baseline: 3.89 ± 1,78, 9 months: 2.74 ± 1.39). Increase in control group (baseline: 2.81 ± 1.15; 9 months: 3.90 ± 1.45).		

Appendix Table 3: Continued.

Author	**Butt [2]**		
Year	2015		
Country	Malaysia		
Objective	To evaluate the impact of a pharmacist led diabetes management program on type 2 diabetes patients on HbA1c, medication adherence and quality of life.		
Study setting	Secondary endocrine clinic		
Study design	Parallel randomized controlled trial		
Follow-up period	6 months		
Sample	N	73	
		Intervention	Control
	Sex (% male)	39.4	42.4
	Age (years ± SD)	57.4 ± 7.2	57.1 ± 10.8
	Baseline HbA1c (% ± SD)	9.66 ± 1.57	9.64 ± 1.41
	Comorbidities	Not reported	
Intervention			
Description	Patient Education by Pharmacist Program (PEPP). At enrolment: counselling about diabetes, its complications, medication, lifestyle modifications, and self-monitoring. Second visit; reinforcement of the intervention about the lifestyle modifications, mediation adherence, and self-monitoring. In addition, pharmacist assessed the knowledge of the patients about diabetes and complication components of education and repeated the intervention if the pharmacist felt the need for it after assessment.		
Frequency of meetings	3 visits		
Duration of meetings	In total 55-75 minutes		
Intervention team	Pharmacist		
Education intervention team	No		
Intervention topics	Diabetes education, medication, lifestyle, self-monitoring blood glucose, other		
Control group			
Description	Standard care; patient-physician meeting every 4-9 months. Pharmacy care during prescription refills every 2-3 months.		
Outcomes			
Clinical outcomes	HbA1c, fasting blood glucose, lipid profile, BMI		
Patient reported outcomes	Medication adherence (Morisky scale), QoL (EQ5D-3L), diabetes knowledge		
Results			
Clinical results	HbA1c: Statistical significant decline in intervention group compared to control group. BMI: Statistical significant decrease in intervention group, however no significant change between control and intervention group.		
Patient reported results	Medication adherence: Statistical significant improvement in intervention group and compared to control group. Non-significant change within control group. QoL: Statistical significant change within intervention group for mobility and anxiety as well as for the overall score. Changes in intervention group were statistical significant compared to the changes in the control group.		
Author	**Cani [3]**		
Year	2015		
Country	Brazil		
Objective	To support informed decision-making, self-care behaviors, problem-solving and active collaboration with the health care team to improve clinical outcomes, health status and quality of life.		

Appendix Table 3: Continued.

Study setting	Diabetes outpatient clinic		
Study design	Parallel randomized controlled trial		
Follow-up period	6 months		
Sample	N	78	
		Intervention	Control
	Sex (% male)	38.2	38.9
	Age (years ± SD)	61.9 ± 9.6	61.6 ± 8.1
	Baseline HbA1c (% ± SD)	9.78 ± 1.55	9.61 ± 1.38
	Comorbidities	Not reported	
Intervention			
Description	Individualized pharmacotherapeutic care plan (PCP), designed based on necessities identified in the first interview; indication, proper dosage, side effects, storage. Pill organizers were given along with verbal directions on their assembly. Diabetes education; complications, lifestyle changes, regular foot inspections, home blood glucose monitoring. Also written guidance was provided.		
Frequency of meetings	6 visits		
Duration of meetings	Not reported		
Intervention team	Pharmacist		
Education intervention team	Not reported		
Intervention topics	Diabetes education, medication, lifestyle, self-monitoring blood glucose, other		
Control group			
Description	Observed at initial and final assessment. Control patients received standard care. Although they did not receive advice from a clinical pharmacist, they were allowed to request information anytime during the study period.		
Outcomes			
Clinical outcomes	HbA1c		
Patient reported outcomes	Self-reported adherence (Morisky-Green questionnaire and Adherence to Medicine Questionnaire (AMQ)), insulin injection, home blood glucose monitoring, QoL (Diabetes Quality of Life Measure), diabetes knowledge.		
Results			
Clinical results	HbA1c: Statistical significant decrease within intervention group (baseline; 9.78 ± 1.55, final; 9.21 ± 1.41). No statistical significant difference between control and intervention at final measurement.		
Patient reported results	Statistical significant improvement of diabetes knowledge, medication knowledge, adherence (Morisky-Green), insulin injection technique, home blood glucose monitoring and QoL within the intervention group as well as between control and intervention group at final measurement.		
Author	**Choe [4]**		
Year	2005		
Country	U.S.		
Objective	To evaluate the effect of case management by a clinical pharmacist on glycemic control and preventive measures in patients with type 2 diabetes.		
Study setting	Ambulatory care clinic		
Study design	Parallel randomized controlled trial		
Follow-up period	12-24 months		

Appendix Table 3: Continued.

Sample	N	80	
		Intervention	Control
	Sex (% male)	48.8	46.1
	Age (years ± SD)	52.2 ± 11.2	51.0 ± 9.0
	Baseline HbA1c (% ± SD)	10.1 ± 1.8	10.2 ± 1.7
	Comorbidities	Not reported	
Intervention			
Description	Clinical pharmacist as case manager for intervention patients. Therapeutic regiments were evaluated based on efficacy, safety, adverse effects, drug interactions, drug costs and monitoring. Patients had an initial visit with pharmacist (approx. 1 hour), assessment of medication management, basic education regarding diabetes self-management skills (importance of self-care, medication and screening process). Subsequent visits based upon patient's needs. Monthly telephone calls. Clinical pharmacist periodically reviewed the status of all intervention patients and provided condensed "diabetes status updates" to providers using a standardized form.		
Frequency of meetings	12 visits/telephone calls		
Duration of meetings	Not reported		
Intervention team	Pharmacist		
Education intervention team	Not reported		
Intervention topics	Medication, self-management skills, other.		
Control group			
Description	Controls only received regular care including regular follow-up visits with primary care physicians. No special contact during the intervention and no exit interviews or process measurements at the end of the study.		
Outcomes			
Clinical outcomes	HbA1c, LDL, dilated retinal examination, urine micro albumin screening, monofilament testing for diabetic neuropathy.		
Patient reported outcomes	None		
Results			
Clinical results	HbA1c: Decrease of HbA1c in both intervention and control group. Statistical significant difference between groups at final measurement. LDL measurement, retinal examination within 2 years and documented monofilament examination for neuropathy occurred more frequently among those in the intervention group compared with the control group.		
Patient reported results	N/A		
Author	**Cohen [5]**		
Year	2011		
Country	U.S.		
Objective	To assess the efficacy of adding a pharmacist-led intensive behavioral and pharmacologic SMA intervention – namely, the Veterans Affairs (VA) Multidisciplinary Education and Diabetes Intervention for Cardiac Risk Reduction-Extended (MEDIC-E) – to standard primary care, as compared to standard primary care alone for the treatment of patients with type 2 diabetes and associated cardiovascular risk factors over a 6 month period.		
Study setting	Veterans affairs medical center		
Study design	Parallel randomized controlled trial		
Follow-up period	6 months		

Appendix Table 3: Continued.

Sample	N	103	
		Intervention	Control
	Sex (% male)	100	96
	Age (years ± SD)	69.8 ± 10.7	67.2 ± 9.4
	Baseline HbA1c (% ± SD)	7.8 ± 1.0	8.1 ± 1.4
	Comorbidities	Heart failure, stroke, coronary heart disease, COPD, mood disorder	
Intervention			
Description	4 once-weekly 2-hour sessions followed by 5 monthly booster sessions held in a classroom with approximately 4-6 participants in each session. Sessions consisted of two parts; education in the first half and behavioral and pharmacologic interventions for hypertension, hyperlipidemia, and hyperglycemia and tobacco use in the second half. Topics discussed: diabetes basics, symptomatology, hypertension, dyslipidemia, tobacco use, target goals for each condition, chronic complications, risk factor control, obstacles, solutions, treatment plans for diet, exercise, monitoring and other self-care behaviors.		
Frequency of meetings	First month; 4 weekly meetings. Thereafter 5 monthly meetings.		
Duration of meetings	Weekly visits; 120 minutes Monthly visits; 90 minutes		
Intervention team	Pharmacist, dietitian, nurse, physical therapist		
Education intervention team	Not reported		
Intervention topics	Diabetes education, medication, lifestyle, individual care plan/goal setting, self-management skills, self-monitoring blood glucose, other.		
Control group			
Description	Standard primary care; individual clinic visits with primary care providers once every 4 months. Visits take 20-60 minutes per appointment.		
Outcomes			
Clinical outcomes	HbA1c, blood pressure, LDL, HDL, triglycerides, total cholesterol		
Patient reported outcomes	QoL (SF-36 for veterans), 4-question of perceived competence, summary of diabetes self-care activities questionnaire (SDSCA)		
Results			
Clinical results	HbA1c: Statistical significant reduction within the intervention group. After 6 months 40.8% of the intervention group achieved target goals for HbA1c compared to 20.4% in the control group. Blood pressure: Statistical significant reduction of systolic blood pressure (SBP) in the intervention group. After 6 months 58% of the intervention group and 32.7% of the control group achieved goals for SBP. After 6 months there was also a statistical significant difference between intervention and control group. LDL: At baseline a statistical significant lower level of LDL in the intervention group (96.1 ±25.4 mg/dl) compared to control group (110.7 ± 37.2 mg/dl). After 6 months a statistical significant reduction in the intervention group compared to baseline. Total cholesterol: At baseline a statistical significant lower level in the intervention group (165.1 ± 34.0 mg/dl) compared to control group (180.7 ± 37.2 mg/dl).		
Patient reported results	QoL: No statistical significant difference from baseline to follow-up in either physical or mental score. Perceived competence: No statistical significant difference from baseline to follow up. SDSCA: Statistical significant increase in the number of days per week for following directions for testing blood glucose for both the intervention and control group. Foot care; the number of days of the week that patients followed foot-care recommendations was statistical significant higher in the intervention group but not for the control group.		

Appendix Table 3: Continued.

Author	**Doucette [6]**		
Year	2009		
Country	U.S.		
Objective	To evaluate the effect of community-pharmacist provided extended diabetes care service on primary clinical outcomes; HbA1c, LD-C, BP, and patients' reported self-care activities.		
Study setting	Community pharmacy		
Study design	Parallel randomized controlled trial		
Follow-up period	12 months		
Sample	N	78	
		Intervention	Control
	Sex (% male)	41.7	47.6
	Age (years ± SD)	58.7 ± 13.3	61.2 ± 10.9
	Baseline HbA1c (% ± SD)	7.99 ± 1.45	7.91 ± 1.91
	Comorbidities	Not reported	
Intervention			
Description	Role pharmacist: gathering information, evaluation the information, formulating a plan, implementing the plan, monitoring the plan, follow-up with patient and physician. During the first visit: pharmacist takes patient's history, create a medication list, assess clinical markers, review medication and self-care behaviors, and identify drug therapy problems. Subsequent visits were intended to allow pharmacists to follow-up on previous problems, identify new problems, reassess clinical parameters, and discuss self-care activities.		
Frequency of meetings	Up to 4 meetings		
Duration of meetings	Not reported		
Intervention team	Pharmacist		
Education intervention team	Yes, self-study of approximately 15 hours.		
Intervention topics	Medication, individual care plan/ goal setting, self-management skills, other		
Control group			
Description	Not reported		
Outcomes			
Clinical outcomes	HbA1c, blood pressure, lipid profile		
Patient reported outcomes	Diabetes self-care questionnaire		
Results			
Clinical results	HbA1c: Non-significant improvement in intervention group. No significant differences between control and intervention groups. Blood pressure: Significant increase in intervention group. No significant differences between intervention and control group. LDL: Statistical significant decrease in both groups. No significant difference between the groups.		
Patient reported results	Diabetes self-care: Statistical significant improvement in intervention group.		
Author	Farsaei [7]		
Year	2011		
Country	Iran		
Objective	To evaluate the effect of a clinical pharmacist-led patient education program for type 2 diabetic patients.		
Study setting	Isfahan endocrine and metabolism research center		
Study design	Parallel randomized controlled trial		
Follow-up period	3 months		

Appendix Table 3: Continued.

Sample	N	174	
		Intervention	Control
	Sex (% male)	36.8	31.8
	Age (years ± SD)	53.4 ± 9.8	52.9 ± 8.5
	Baseline HbA1c (% ± SD)	9.3 ± 1.7	8.9 ± 1.1
	Comorbidities	Hypertension, dyslipidemia, heart disease, thyroid disease, renal disease	
Intervention			
Description	Standard care + pharmacist intervention. Intervention consists of two sessions. First session general extended diabetes education, including difference classifications anti-hyperglycemic agents, dosages, mechanisms of action, indications, efficacy, adverse effects, medication safety issues, contraindications, warnings/precautions, drug interactions, pregnancy risk factors, lactation and storage. Second session: adherence and self-management. After the second session patients received a pill box and diabetes diary log. Individualized patient schedule, medication adherence, dietary adherence, exercise.		
Frequency of meetings	Two education sessions, weekly telephone calls, appointments for glycemic control		
Duration of meetings	Not reported		
Intervention team	Pharmacist		
Education intervention team	Not reported		
Intervention topics	Medication, lifestyle, individual care plan/ goal setting, self-management skills, other		
Control group			
Description	Education program offered by nurse; definition of diabetes, diet therapy, controlling measures, symptoms and control of hypo/hyper, and diabetes complications.		
Outcomes			
Clinical outcomes	HbA1c, fasting blood glucose		
Patient reported outcomes	None		
Results			
Clinical results	HbA1c: Statistical significant reduction in the intervention group. Fasting blood glucose: Statistical significant reduction in the intervention group. No changes in the control group.		
Patient reported results	N/A		
Author	**Jacobs [8]**		
Year	2012		
Country	U.S.		
Objective	To demonstrate that pharmacists working with physicians in an ambulatory care setting can improve glucose, blood pressure, and lipid control for patients with diabetes type 2. Secondary: whether patients adhered to screening and general preventive measures.		
Study setting	Outpatient clinic		
Study design	Parallel randomized controlled trial		
Follow-up period	12 months		
Sample	N	257	
		Intervention	Control
	Sex (% male)	68	55
	Age (years ± SD)	62.7 ± 10.8	63.0 ± 11.2
	Baseline HbA1c (% ± SD)	9.5 ± 1.1	9.2 ± 1.0
	Comorbidities	Retinopathy, nephropathy, neuropathy	
Intervention			

Appendix Table 3: Continued.

Description	Patients had to attend a minimum of 3 clinic visits with a clinical pharmacist (baseline; 6 months, 12 months). Intervention content: comprehensive medication review, physical assessment (weight, height, blood pressure, pulse, foot exam), education on diabetes pathophysiology and importance of control, ordering lab tests; reviewing, modifying and monitoring of mediation therapy and providing detailed counselling on all therapies; self-monitoring blood glucose; dietary guidelines and exercise.		
Frequency of meetings	Minimal 3 visits		
Duration of meetings	Not reported		
Intervention team	Pharmacist		
Education intervention team	No		
Intervention topics	Diabetes education, medication, lifestyle, individual care plan/ goal setting, self-management skills, other		
Control group			
Description	Usual care directed by physician. Not specified.		
Outcomes			
Clinical outcomes	HbA1c (target ≤7%), LDL cholesterol (target ≤100 mg/dl), blood pressure (target ≤ 130/80 mm Hg)		
Patient reported outcomes	None		
Results			
Clinical results	HbA1c: Statistical significant decrease in intervention group compared to control (7.7% vs. 8.4%). In intervention group 35% of the participant met the target value (≤ 7%) and 21% in the control group (measured after 12 months). No statistical significant difference between groups. LDL: Statistical significant decrease in intervention group compared to control group (93.7 vs 105.1 mg/dl). 62% of the intervention group met target values. No statistical significant difference between groups. Blood pressure: systolic blood pressure (SBP) was significantly higher in intervention group at baseline. SBP decreased in both groups, though no statistical significant difference between groups after 12 months. 51% of intervention an d43% of the control group met target values for SBP. Diastolic blood pressure (DBP) statistical significant decreased more in intervention group than in control group (72.0 vs 77.6 mm Hg). 84% in intervention and 77% in control group met target after 12 months.		
Patient reported results	N/A		
Author	**Jahangard-Rafsanjani [9]**		
Year	2015		
Country	Iran		
Objective	To evaluate the effect of a community pharmacist's diabetes support program on patients with type 2 diabetes receiving specialty care in a middle-income country.		
Study setting	Community pharmacy		
Study design	Parallel randomized controlled trial		
Follow-up period	5 months		
Sample	N	101	
		Intervention	Control
	Sex (% male)	51	48
	Age (years ± SD)	57.3 ± 8.6	55.9 ± 8.7
	Baseline HbA1c (% ± SD)	7.6 ± 1.6	7.51 ± 1.8
	Comorbidities	Not reported	
Intervention			

Appendix Table 3: Continued.

Description	The program consisted of 5 follow-up visits with the community pharmacist (once a month). Each visit was estimated to be 30 minutes. The community pharmacist made a telephone call between visits to reinforce treatment adherence and resolve any therapy-related problems. Education on diet management, physical activity, diabetes complications. As well as information regarding individual needs. Every follow-up visit medication related problems, self-care issues, and logbook were discussed. Patients were also taught how to self-monitor blood glucose.		
Frequency of meetings	5 visits		
Duration of meetings	30 minutes		
Intervention team	Pharmacist		
Education intervention team	Yes		
Intervention topics	Diabetes education, lifestyle, individual care plan/ goal setting, self-management skills, self-monitoring blood glucose, other		
Control group			
Description	Usual care from physician. At the end of the study they received brief education from the community pharmacist.		
Outcomes			
Clinical outcomes	HbA1c, blood pressure, weight, BMI		
Patient reported outcomes	Adherence (Morisky), self-care activity (SDSCA), physician visits		
Results			
Clinical results	HbA1c: Statistical significant reduction in both intervention and control group. No significant difference between groups. Systolic blood pressure (SBP): No difference within and between groups. Diastolic blood pressure (DBP): No difference within and between groups. BMI: No statistical significant difference between groups at baseline, at follow-up BMI statistical significant lower in intervention group compared to control.		
Patient reported results	Adherence: Statistical significant improvement in intervention group (51% to 24%). Self-care activity: Statistical significant improvement in intervention group for general diet, blood glucose monitoring and foot care. Physician visits: statistical significant more patients in intervention group visited their physician at least once (71.7% vs. 32.5%).		
Author	**Jameson [10]**		
Year	2010		
Country	U.S.		
Objective	To investigate the effect of pharmacist management of poor controlled diabetes mellitus in a community base primary care group.		
Study setting	Primary care clinic		
Study design	Parallel randomized controlled trial		
Follow-up period	12 months		
Sample	N	104	
		Intervention	Control
	Sex (% male)	48.9	49
	Age (years ± SD)	49.3 ± 10.8	49.7 ± 10.9
	Baseline HbA1c (% ± SD)	10.4 ± 1.2	11.1 ± 1.6
	Comorbidities	Not reported	
Intervention			

Appendix Table 3: Continued.

Description	One pharmacist provided all diabetes-relate care for the intervention group. All intervention patients received individualized education regarding diabetes self-management, including diet, exercise, blood glucose level testing, medications, and insulin. The number of subsequent visits was based on the need for further education. Follow-up visits were supplemented with telephone calls as needed for medication management.		
Frequency of meetings	On average 6 visits and 3 telephone calls		
Duration of meetings	Visit: 30-60 minutes. Telephone call: 10-20 minutes.		
Intervention team	Pharmacist		
Education intervention team	No		
Intervention topics	Medication, lifestyle, self-management skills, self-monitoring blood glucose		
Control group			
Description	Not reported		
Outcomes			
Clinical outcomes	HbA1c (after 1 year and the percentage of patients with a 1.0% decrease)		
Patient reported outcomes	Number of pharmacist visits		
Results			
Clinical results	HbA1c: Overall median reduction in the intervention group was 1.1%. Not statistical significant compared to control group.		
Patient reported results	Pharmacist visits: On average 6 pharmacy visits and 3 telephone calls over the course of a year.		
Author	**Jarab [11]**		
Year	2012		
Country	Jordan		
Objective	To evaluate the impact of a clinical pharmacist-led pharmaceutical care program on different clinical outcomes and self-management behavior in outpatients with DM2 in Jordan.		
Study setting	Outpatient clinic		
Study design	Parallel randomized controlled trial		
Follow-up period	6 months		
Sample	N	171	
		Intervention	Control
	Sex (% male)	57.6	55.8
	Age (years ± SD)	63.4 ± 10.1	65.3 ± 9.2
	Baseline HbA1c (% ± SD)	8.5	8.4
	Comorbidities	Not reported	
Intervention			
Description	Structured education and discussion considering: diabetes, complications, prescribed drug therapy, dosage, side effects, adherence. Special attentions for lifestyle management (patients were encouraged to change unhealthy diets, perform regularly physical activities, monitoring blood glucose levels). Smoking cessation was discussed. A booklet with all information regarding the education was provided to the patients. During 8 weeks the patients were weekly telephoned to discuss and review the education aspects and answer questions.		
Frequency of meetings	At least 1 visit and 8 telephone calls		
Duration of meetings	Duration of visit unknown, telephone calls approximately 20 minutes.		
Intervention team	Clinical pharmacist		

Appendix Table 3: Continued.

Education intervention team	Not reported		
Intervention topics	Diabetes education, medication, lifestyle, self-monitoring blood glucose, other		
Control group			
Description	Usual care by medical and nursing staff; patient assessment, a 3-6 month review to measure blood glucose, give advice on self-monitoring blood glucose, and nutrition counseling.		
Outcomes			
Clinical outcomes	HbA1c, blood pressure, lipid profile, BMI		
Patient reported outcomes	Adherence (Morisky), self-care activity (SDSCA)		
Results			
Clinical results	HbA1c: Statistical significant reduction in intervention group and between intervention and control group. In the control group was an increase of HbA1c. Blood pressure: Statistical significant reduction of blood pressure between the intervention and the control group. Lipids: No significant improvement in HDL-C levels between the two groups		
Patient reported results	Adherence: No significant difference between groups over the course of the study. SDSCA: Statistical significant improvement in intervention group for diet, exercise and self-monitoring blood glucose compared to control group.		
Author	**Kjeldsen [12]**		
Year	2015		
Country	Denmark		
Objective	To investigate whether a comprehensive and a brief individually targeted intervention for patients with type 2 diabetes could improve implementation of drug therapy in Danish community pharmacies. The intervention intended to give patients more competence and support to improve adherence and self-management in order to reach treatment goals for diabetes and blood pressure as well as goals for patient perceived outcomes.		
Study setting	Community pharmacy		
Study design	Parallel randomized controlled trial		
Follow-up period	6 months		
Sample	N	205	
		Intervention	Control
	Sex (% male)	57.9 (basic intervention), 59.5 (extended intervention)	62.4
	Age (years ± SD)	63 ± 8.8 (basic), 63.4 ± 7.8 (extended)	62.1 ± 10.2
	Baseline HbA1c (% ± SD)	Not reported	Not reported
	Comorbidities	Not reported	
Intervention			
Description	Two interventions were tested; basic intervention (BI) and extended intervention (EI). Key elements for both interventions were; 1. Quick screening for non-adherence and identification of problem types. 2. Patient narratives (story-telling) as the key starting point. 3. Assessment and possibly adjustment of drug therapy. 4. Finding resources in the system around the problem and the patient (the patient's system). 5. Dialog based on motivational interview or individual coaching, in order to tailor solutions to individual needs and resources. 6. Offering relevant reminder technology and/or patient instruction. 7. Follow-up. 8. Close collaboration with patient's GP.		
Frequency of meetings	At least 4 visits		

Appendix Table 3: Continued.

Duration of meetings	In total 65-130 minutes		
Intervention team	Pharmacy assistant and pharmacist		
Education intervention team	Yes		
Intervention topics	Medication, individual care plan/ goal setting, other		
Control group			
Description	No information		
Outcomes			
Clinical outcomes	Blood glucose, blood pressure, HbA1c, lipid profile		
Patient reported outcomes	Adherence, problems, health related quality of life (HRQoL) (EQ-5D), knowledge about diabetes, perceived competence for diabetes (PCDS), perceived concordance, self-efficacy, hospital admissions, consultations with doctors.		
Results			
Clinical results	Blood glucose: Non-significant decrease of blood glucose in both intervention groups. Blood pressure: Statistical significant decrease of systolic blood pressure within the extended intervention group. HbA1c: Not enough results for analysis Lipids: Not enough results for analysis.		
Patient reported results	Concordance: 86% of the participants would like to be actively involved in decision making about their treatment, 85% was satisfied with the decisions made, 55% is sufficiently asked about their treatment. Knowledge: Statistical significant improvement of knowledge in the EI group, no statistical significant difference between BI and control. Most frequently delivered technical adherence and self-management improving interventions were self-monitoring of blood glucose, use of diary, use of individual reminder systems, and introduction of dose administration aids.		
Author	**Korcegez [13]**		
Year	2017		
Country	Cyprus		
Objective	To evaluate the effect of a pharmacist-led care program in a public hospital's outpatient diabetes clinic on the clinical outcome of glycemic control, determined primarily by A1c.		
Study setting	Hospital outpatient diabetes clinic		
Study design	Parallel randomized controlled trial		
Follow-up period	12 months		
Sample	N	152	
		Intervention	Control
	Sex (% male)	22.7	26.0
	Age (years ± SD)	61.80 ±10.38	62.22 ±9.54
	Baseline HbA1c (% ± SD)	8.29 ±0.89	8.31 ±0.84
	Comorbidities	Hypertension, dyslipidemia, thyroid disease, rheumatoid arthritis, asthma, heart failure, osteoporosis, psychological disorders	
Intervention			
Description	The pharmacist's face-to-face education and discussion sessions included revision of medication, as necessary, and the sharing of diabetes knowledge, clinical goals and self-care activities. The purpose of the pharmacist-led care program was the educate patients regarding the correct use of medication and reinforce adherence to treatment, along with developing patient knowledge of drug therapy and health conditions.		
Frequency of meetings	5 meetings in 12 months		
Duration of meetings	NR		

Appendix Table 3: Continued.

Intervention team	Pharmacist		
Education intervention team	NR		
Intervention topics	Diabetes, medication, lifestyle, medication review, written information, individual care plan/ goal setting, self-management, self-monitoring blood glucose		
Control group			
Description	Control group patients met with the research pharmacist at baseline and at the end of 12 months to collect laboratory and questionnaire data. Control group patients received standard care provided by the outpatient diabetes clinic, consisting of appointments with physicians every 4-8 weeks to renew prescriptions for their medicines during the study period.		
Outcomes			
Clinical outcomes	Fasting blood glucose, HbA1c, lipid profile, blood pressure, weight		
Patient reported outcomes	Adherence (Morisky Green), self-care (SDSCA)		
Results			
Clinical results	Fasting blood glucose: Significant reduction within intervention and control group, no between group differences. HbA1c: Significant greater reduction in intervention group compared to control (-0.74% vs. -0.04%). Blood pressure: Systolic- and diastolic blood pressure decreased significantly in intervention group compared to control. Lipid profile: Significant improvement in total cholesterol in intervention group compared to control group. Significant reduction of HDL-C levels within intervention group.		
Patient reported results	Adherence: Significant improvement within intervention group. Self-care: Significant improvement in intervention group compared to control for total diet, blood glucose measurement, and foot care.		
Author	**Kraemer [14]**		
Year	2012		
Country	U.S.		
Objective	To determine whether counseling by community pharmacists that provides patient education, goal setting, monitoring, and coaching can better improve patient self-management of diabetes as measured by HbA1c concentrations compared to the distribution of written educational materials without pharmacist counseling.		
Study setting	Outpatient clinic		
Study design	Parallel randomized controlled trial		
Follow-up period	12 months		
Sample	N	69	
		Intervention	Control
	Sex (% male)	61.1	38.7
	Age (years ± SD)	55.6 ± 6.8	52.6 ± 9.2
	Baseline HbA1c (% ± SD)	7.28	7.38
	Comorbidities	Not reported	
Intervention			
Description	Counseling by pharmacist. Pharmacists were trained in gathering patient information, educating and coaching patients and document outcomes. Pharmacists were requested to send a progress note to the GP after each visit.		
Frequency of meetings	On average 5.4 meetings		
Duration of meetings	Not reported		
Intervention team	Pharmacist		

Appendix Table 3: Continued.

Education intervention team	Yes		
Intervention topics	Individual care plan/goal setting, self-management skills, self-monitoring blood glucose		
Control group			
Description	Written education information about managing diabetes and additional information was mailed after 3 months. At the start and end of the study also for the control patients, blood pressure, weight, waist circumference, HbA1c, serum glucose and lipid spectrum were measured.		
Outcomes			
Clinical outcomes	HbA1c, lipid profile, fasting blood glucose, blood pressure, weight, waist circumference, BMI		
Patient reported outcomes	The diabetes empowerment scale (DES), The diabetes knowledge test (DKT), Adherence starts with knowledge (ASK-20)		
Results			
Clinical results	HbA1c: Statistical significant decrease in intervention group of 0.5% and non-significant decrease of 0.17% in control group. No significant difference between intervention and control group at final follow-up. HDL-C: Statistical significant decrease in both groups, but no significant decrease between groups. No statistical significant changes for blood pressure, weight, waist circumference, and BMI.		
Patient reported results	Adherence: No significant changes. Diabetes empowerment: Statistical significant improvement of scores within the intervention group, no significant differences between intervention and control group.		
Author	**Krass [15]**		
Year	2007		
Country	Australia		
Objective	To assess the impact of a community pharmacy diabetes service model on patient outcomes in type 2 diabetes.		
Study setting	Community pharmacy		
Study design	Cluster randomized controlled trial		
Follow-up period	6 months		
Sample	N	335	
		Intervention	Control
	Sex (% male)	51	51
	Age (years ± SD)	62 ± 11	62 ± 11
	Baseline HbA1c (% ± SD)	8.9 ± 1.4	8.3 ± 1.3
	Comorbidities	Hypertension, high-cholesterol	
Intervention			
Description	Elements of intervention: Review of self-monitoring of blood glucose; disease, medication and lifestyle education; adherence support and detection of drug-related problems; referrals to GP when appropriate. First visit: blood glucose meter, conversation with patient and additional information supply if needed about adherence, self-management, lifestyle changes regarding weight loss and physical activity. At every meeting individual goals were set and progress discussed during the next meeting.		
Frequency of meetings	5 visits		
Duration of meetings	Not reported		
Intervention team	Pharmacist		
Education intervention team	Yes		

Appendix Table 3: Continued.

Intervention topics	Diabetes education, medication, lifestyle, individual care plan/ goal setting, self-management skills, self-monitoring blood glucose, other		
Control group			
Description	Usual care, no specialized diabetes service in the pharmacy.		
Outcomes			
Clinical outcomes	HbA1c, blood pressure, lipid profile, BMI		
Patient reported outcomes	Quality of life (EQ-5D)		
Results			
Clinical results	HbA1c: Decrease in intervention group 0.97% and in control group 0.27%. Statistical significant larger reduction in intervention group compared to control. Blood glucose: Statistical significant reduction within intervention group from 9.4 mmol/L to 8.5 mmol/L. Blood pressure: Systolic blood pressure (SBP) in intervention group statistical significant decrease from 143 mm Hg to 137 mm Hg. Diastolic blood pressure (DBP) in intervention group statistical significant decrease from 82 mm Hg to 79 mm Hg. Changes in SBP and DBP were non-significant compared to control. Lipid profile: Statistical significant improvement in both groups, but no significant difference between intervention and control group.		
Patient reported results	Quality of life: Statistical significant improvements in quality of life in the intervention group as indicated by increases in ED-5D health-state scale scores. Though changes on EQ-5D showed no significant difference.		
Author	**Mehuys [16]**		
Year	2011		
Country	Belgium		
Objective	To study the effectiveness and sustainability of effects of a community pharmacist intervention in diabetes care. Primary outcome: glycemic control. Secondary outcomes: adherence, knowledge about diabetes and self-management.		
Study setting	Community pharmacy		
Study design	Cluster randomized controlled trial		
Follow-up period	6 months		
Sample	N	288	
		Intervention	Control
	Sex (% male)	51.0	53.7
	Age (years ± SD)	63	62.3
	Baseline HbA1c (% ± SD)	7.7	7.3
	Comorbidities	Not reported	
Intervention			
Description	Protocol defined intervention at the start of the study and each prescription refill visit. Topics discussed; education about type 2 diabetes and complications, education about correct use of oral hypoglycemic agents, medication adherence, healthy lifestyle education (diet, physical exercise, smoking cessation), reminders about annual eye and foot examination.		
Frequency of meetings	Visit at start and at each prescription- refill visit		
Duration of meetings	Not reported		
Intervention team	Pharmacist		
Education intervention team	Yes		
Intervention topics	Diabetes education, medication, lifestyle.		

Appendix Table 3: Continued.

Control group			
Description	Usual care by pharmacist		
Outcomes			
Clinical outcomes	Fasting plasma glucose, HbA1c		
Patient reported outcomes	Adherence, knowledge about diabetes (Brief diabetes knowledge test of the Michigan diabetes research and training center), self-management (SDSCA)		
Results			
Clinical results	Fasting plasma glucose: Statistical significant reduction in both intervention and control group. No significant difference between groups. HbA1c: Statistical significant reduction in intervention group and compared to control group.		
Patient reported results	Knowledge: Statistical significant improvement in intervention group and between groups. Self-management: No improvement in control group. Statistical significant improvement in intervention group for specific diet, physical exercise and foot care. Between group difference for physical exercise and foot care.		
Author	**Nascimento [17]**		
Year	2015		
Country	Portugal		
Objective	To evaluate the improvement on self-care after an intervention based on the management of pharmacotherapy of diabetes associated with therapeutic education in elderly patients following an at home regime.		
Study setting	Diabetes care clinic		
Study design	Parallel randomized controlled trial		
Follow-up period	6 months		
Sample	N	90	
		Intervention	Control
	Sex (% male)	56.8	58.1
	Age (years ± SD)	74.2 ± 5.4	72.3 ± 4.5
	Baseline HbA1c (% ± SD)	8.6 ± 1.2	8.2 ± 0.7
	Comorbidities	Hypertension, dyslipidemia, vascular complications	
Intervention			
Description	Individualized pharmacotherapy management with the analysis of necessity, safety and effectiveness of medications taken by patients. Individualized therapeutic education on diabetes care and especially on the patient's pharmacotherapy.		
Frequency of meetings	At least 2 visits		
Duration of meetings	Not reported		
Intervention team	Not specified		
Education intervention team	Not reported		
Intervention topics	Medication, self-management skills		
Control group			
Description	Standard medical care consultation		
Outcomes			
Clinical outcomes	Fasting blood glucose, HbA1c		
Patient reported outcomes	Adherence to drug therapy (self-reported), adherence to self-assessed care (SDSCA)		
Results			

Appendix Table 3: Continued.

Clinical results	Fasting blood glucose: Statistical significant decrease in intervention group compared to control. Intervention 167.4 ± 39.9 mg/dL to 117.3 ± 26.8 mg/dL. Control 162.33 ± 28.0 mg/dL to 142.2 ± 32.9 mg/dL. HbA1c: Statistical significant decrease in intervention group compared to control. Intervention 8.6 ± 1.2% to 7.7 ± 0.8%. Control 8.2 ± 0.7% to 7.99 ± 0.67%.		
Patient reported results	Adherence to drug therapy: Intervention group 5.6 ± 0.3 to 5.9 ± 0.1. Control group 5.1 ± 0.78 to 5.7 ± 0.3. Self-assessed care: In the intervention group statistical significant improvements for general diet, specific diet, exercise, blood glucose management.		
Author	**Odegard [18]**		
Year	2005		
Country	U.S.		
Objective	To assess the effect of a pharmacist's intervention on diabetes control as determined by HbA1c. The effects of pharmacist intervention on change in diabetes medication appropriateness and adherence were assessed as secondary outcomes.		
Study setting	University primary care clinic		
Study design	Parallel randomized controlled trial		
Follow-up period	6-12 months		
Sample	N	77	
		Intervention	Control
	Sex (% male)	52	64
	Age (years ± SD)	51.6 ± 11.6	51.9 ± 10.4
	Baseline HbA1c (% ± SD)	10.2 ± 0.8	10.6 ± 1.4
	Comorbidities	Not reported	
Intervention			
Description	Community pharmacist formulated diabetes care plan (DCP) with patient and implements it. Week 1-4: intensive intervention phase, weekly phone call of clinic visit to follow up on DCP, modify as needed, make necessary referrals. Months 1-6: maintenance phase, phone call or clinic visit (weekly or monthly based on needs acuity) to assess DCP progress, reactivate intensive phase (weekly) for new problems or changes in therapy. Months 7-12: resumption of usual care end of clinical pharmacist follow-up.		
Frequency of meetings	On average 2.1 ± 1.0 visits and 4.5 ± 1.9 telephone calls		
Duration of meetings	Visits 30 minutes, telephone calls 10 minutes.		
Intervention team	Pharmacist		
Education intervention team	Not reported		
Intervention topics	Medication, lifestyle, individual care plan/ goal setting, self-management skills, self-monitoring blood glucose, other.		
Control group			
Description	Usual care; subjects were instructed to continue normal care with their primary care provider. Diabetes education was not provided during the baseline interview to avoid introducing an intervention for patients in the control group.		
Outcomes			
Clinical outcomes	HbA1c		
Patient reported outcomes	Medication appropriateness (MAI), self-reported adherence, contact moments with pharmacist, self-management, diabetes knowledge, quality of life.		
Results			
Clinical results	HbA1c: Statistical significant decrease within intervention group; baseline 10.2%, 6-months 8.7% and 12 months 8.2%. No significant difference with control group.		

Appendix Table 3: Continued.

Patient reported results	Medication appropriateness: No significant change in medication appropriateness after the intervention. Adherence: Intervention had no effect on adherence. Control patients reported better adherence than intervention patients. Contact with pharmacist: On average patients had 4.5 ± 1.9 telephone contacts with the pharmacist, taking approximately 10 minutes per call and 2.1 ± 1.0 in-person visits of approximately 30 minutes per visit. No results reported for self-management, diabetes knowledge and quality of life.		
Author	**Samtia [19]**		
Year	2013		
Country	Pakistan		
Objective	To assess the impact of pharmacist-led interventions on glycemic control, medication adherence, disease knowledge, and lifestyle modifications among patients with diabetes in Southern Punjab, Pakistan.		
Study setting	Diabetes clinic		
Study design	Parallel randomized controlled trial		
Follow-up period	5 months		
Sample	N	348	
		Intervention	Control
	Sex (% male)	52.8	48.2
	Age (years ± SD)	46.1	42.3
	Baseline HbA1c (% ± SD)	8.51	8.54
	Comorbidities	Not reported	
Intervention			
Description	Intervention group received predefined specialized care regarding; education of disease including complications, adherence and effect on glycemic control, diet, sensory changes and foot examination, exercise, self-monitoring of blood glucose, control of HbA1c values and fasting blood glucose, smoking cessation.		
Frequency of meetings	At least 2 visits		
Duration of meetings	Not reported		
Intervention team	Pharmacist		
Education intervention team	Not reported		
Intervention topics	Diabetes education, medication, lifestyle, self-management skills, self-monitoring blood glucose, other.		
Control group			
Description	Usual medical care		
Outcomes			
Clinical outcomes	Fasting blood glucose, HbA1c, BMI waist circumference, blood pressure		
Patient reported outcomes	Adherence, knowledge regarding disease, self-monitoring, life-style modifications. Smoking, education, diabetes type, medication used.		
Results			
Clinical results	Fasting blood glucose: Statistical significant improvement in intervention group. No significant difference between intervention and control group. HbA1c: Statistical significant improvement in intervention group, no significant difference between intervention and control group. Waist: Statistical significant improvement in the intervention group and between intervention and control group. BMI: Statistical significant improvement in the intervention group and between intervention and control group.		

Appendix Table 3: Continued.

Patient reported results	Adherence: No significant differences within intervention and control group, but statistical significant improvement in intervention group compared to control group. Knowledge and self-care: Statistical significant improvement in the intervention group for "knowledge of sensory changes", "foot care", "self-monitoring blood sugar", "role of exercise" and "dietary restrictions". Statistical significant improvement between groups in favor of intervention for "knowledge regarding sensory changes", "self-monitoring of blood sugar" and "role of exercise". Smoking: Statistical significant increase of the percentage of non-smokers in the intervention group. No significant difference between intervention and control group.		
Author	**Sarkadi [20]**		
Year	2004		
Country	Sweden		
Objective	To investigate the effectiveness of an experience-based group educational program 24 months after baseline and the pinpoint mediators that might play a role in achieving desired metabolic outcomes.		
Study setting	Not reported		
Study design	Parallel randomized controlled trial		
Follow-up period	12 months + final follow up after 24 months		
Sample	N	77	
		Intervention	Control
	Sex (% male)	Not reported	Not reported
	Age (years ± SD)	66.4	66.5
	Baseline HbA1c (% ± SD)	6.45	6.45
	Comorbidities	Not reported	
Intervention			
Description	Practical aspects of diabetes management were discussed including; diet, performing self-monitoring tasks, exercise. All participants in the intervention group received a booklet "how to manage your diabetes" with information regarding; logs of imaginary people, information about complications, personal plan for follow-up visits.		
Frequency of meetings	12 visits		
Duration of meetings	Not reported		
Intervention team	Pharmacist and nurse		
Education intervention team	Yes		
Intervention topics	Diabetes education, medication, lifestyle, self-management skills, self-monitoring blood glucose, other.		
Control group			
Description	No intervention for 12 months. Control group received invitation to participate in educational program 24 months after the start of the initial study.		
Outcomes			
Clinical outcomes	HbA1c, BMI		
Patient reported outcomes	Personal perception of diabetes		
Results			
Clinical results	HbA1c: Statistical significant improvement in intervention group compared to control group after 6 months and 24 months. Control group showed no significant improvement over 24 months.		

Appendix Table 3: Continued.

Patient reported results	Personal perception: Statistical significant improvement in favour of intervention group compared to control for; "being more satisfied with one's own knowledge about diabetes", "exercising more in order to affect blood glucose levels before measurement", "being able to predict current blood glucose levels before measuring it".		
Author	**Shao [21]**		
Year	2017		
Country	China		
Objective	To evaluate the effect of pharmaceutical care on T2DM outpatients		
Study setting	Endocrinology outpatient service		
Study design	Parallel randomized controlled trial		
Follow-up period	6 months		
Sample	N	199	
		Intervention	Control
	Sex (% male)	51.0	47.5
	Age (years ± SD)	58.86 ±10.59	59.20 ±10.34
	Baseline HbA1c (% ± SD)	7.38 ±1.71	7.37 ±1.44
	Comorbidities	NR	
Intervention			
Description	Intervention program included education and interviews. Education consisted of basic knowledge of T2DM, risk of diabetes complications, proper use and precautions of oral antidiabetics and insulin, signs or symptoms of hypoglycemia and self-management, appropriate self-blood glucose monitoring and healthy lifestyle. During the interviews pharmacists discussed with each patient about their medication adherence, self-monitoring of blood glucose, exercise, explained side-effects of drugs and possible drug interactions.		
Frequency of meetings	Two educational sessions (baseline and third month), 3 face-to-face interviews (every other month), 6 telephone interviews (every month)		
Duration of meetings	NR		
Intervention team	Pharmacist		
Education intervention team	NR		
Intervention topics	Diabetes, medication, lifestyle, self-management, self-monitoring blood glucose		
Control group			
Description	Control group received usual care from the medical staff and no additional pharmaceutical care from a clinical pharmacist.		
Outcomes			
Clinical outcomes	Height, weight, blood pressure, fasting blood glucose, postprandial blood glucose 2h (PBG2h), HbA1c, lipids		
Patient reported outcomes	Adherence (Morisky Green)		
Results			

Appendix Table 3: Continued.

Clinical results	Fasting blood glucose: Significant decrease within intervention group and compared to control group. HbA1c: Significant decrease within intervention group and compared to control group. BMI: Significant decrease in both groups, no between group differences. Blood pressure: Systolic blood pressure decreased significantly within intervention group. Diastolic blood pressure significantly decreased in intervention group and increased in control group. Lipids: Total cholesterol significantly decreased in intervention group and compared to control group. Triglycerides decreased significantly within intervention group. LDL-C significantly increased in control group. HDL-C significant reduction in intervention group.		
Patient reported results			
Author	**Taveira [22]**		
Year	2010		
Country	U.S.		
Objective	To assess whether the VA-MEDIC (veterans affairs multi-disciplinary education and diabetes intervention for cardiac risk reduction), a pharmacist-led group medical visit program, could improve achievement of target goals in hypertension hyperglycemia, hyperlipidemia, and tobacco use in patient with type 2 diabetes compared to usual care.		
Study setting	VA (veteran affairs) medical center		
Study design	Parallel randomized controlled trial		
Follow-up period	4 months		
Sample	N	118	
		Intervention	Control
	Sex (% male)	91.4	100
	Age (years ± SD)	62.2 ± 10.3	66.8 ± 10.2
	Baseline HbA1c (% ± SD)	8.5 ± 1.5	7.9 ± 1.1
	Comorbidities	Hypertension, hyperlipidemia, coronary heart disease, congestive heart failure	
Intervention			
Description	4 group sessions with each 2 education parts; education (40-60 minutes) and behavioral and pharmacologic interventions (60-80 minutes). Topics discussed by pharmacist; diabetes overview, prevention of acute complications, goals setting, use of monitoring equipment, smoking cessation, pharmacological case management, report card and review of this diet and weight loss, physical activity.		
Frequency of meetings	4 weekly group visits		
Duration of meetings	120 minutes per visit		
Intervention team	Pharmacist, nutritionist, physical therapist, pharmacist plays a role in 5/8 sessions.		
Education intervention team	Not reported		
Intervention topics	Diabetes education, lifestyle, individual care plan/ goal setting, self-management skills		
Control group			
Description	Usual care provided by primary care providers at VA Medical Center		
Outcomes			
Clinical outcomes	HbA1c, blood pressure, fasting lipids, BMI		
Patient reported outcomes	Self-care behaviors, tobacco use		
Results			

Appendix Table 3: Continued.

Clinical results	HbA1c: Statistical significant decrease in intervention group (0.9%). Also statistical significant compared to control group. Blood pressure: systolic blood pressure statistical significant decrease within intervention group. Diastolic blood pressure statistical significant decrease within intervention group and compared to control group. Lipids: Statistical significant improvement within intervention group. BMI: No significant changes in intervention and control group.		
Patient reported results	Self-care: Statistical significant improvement in intervention group from 64.7% to 82.6%. Greatest improvement in "blood glucose self-monitoring" and "blood pressure self-monitoring". Tobacco use: In the intervention group 3/20 stopped and in control group 0/7 stopped.		
Author	**Taveira [23]**		
Year	2011		
Country	U.S.		
Objective	Whether shared medical appointments (SMAs) are feasible for the treatment of diabetes in patients with depression and to evaluate whether these can be efficacious when led by non-physician professionals (e.g. clinical pharmacist with prescribing authority.		
Study setting	Veterans affairs medical hospital		
Study design	Parallel randomized controlled trial		
Follow-up period	6 months		
Sample	N	88	
		Intervention	Control
	Sex (% male)	100	95.5
	Age (years ± SD)	60.2 ± 9.3	61.4 ± 9.9
	Baseline HbA1c (% ± SD)	8.3 ± 1.7	8.5 ± 1.9
	Comorbidities	Depression (mandatory for participation), coronary artery disease, anxiety, schizophrenia, bipolar, PTSD	
Intervention			
Description	VA-MEDIC-D; 4 once weekly and 5 monthly booster sessions. Each session consisted of two parts; education (40-60 minutes) and behavioral and pharmacologic interventions (60-80 minutes). Each session focusses on self-care behavior, nutrition goals, management of daily aspects of diabetes care through discussion, group counseling. Each participant had their own cardiovascular risk report card. Medication changes if needed (expect for depression). Each participant was provided with a individualized homework.		
Frequency of meetings	4 weekly visits, 4 monthly visits.		
Duration of meetings	Weekly meetings took approximately 120 minutes. No information on the monthly meetings.		
Intervention team	Nurse, nutritionist, clinical pharmacist		
Education intervention team	No		
Intervention topics	Diabetes education, medication, lifestyle, individual care plan/ goal setting, self-monitoring blood glucose and other.		
Control group			
Description	Standard diabetes care with primary care provider, approximately 30 minutes. DSME (diabetes self-management education program) consisting of 4 once weekly meetings and monthly follow-up visits. Care provided by pharmacists, nurses and nutritionists. DSME had similar learning objectives as VA-MEDIC-D.		
Outcomes			
Clinical outcomes	HbA1c, blood pressure, fasting lipid levels		

Appendix Table 3: Continued.

Patient reported outcomes	10 year coronary event risk, depression symptoms, patient health questionnaire (PHQ-9) perceived competence for diabetes (PCDS), diabetes self-care activities (SDSCA), emergency department (ER), smoking, death		
Results			
Clinical results	HbA1c: Statistical significant more participants reached guideline HbA1c in intervention group. Medication: intervention patients were more likely to have medication changes, either in dose increase or initiation of any antihypertensive or antihyperglycemic agent. No significant differences for blood pressure, lipids and smoking.		
Patient reported results	Coronary risk: Statistical significant decrease of the risk in the intervention group. No significant difference between intervention and control group. PCDS: No significant difference within and between intervention and control group. SDSCA: No significant difference within and between intervention and control group. ER: No significant difference within and between intervention and control group. No diabetes related admissions or deaths for either group over the course of the study.		
Author	**Wishah [24]**		
Year	2015		
Country	Jordan		
Objective	To evaluate the impact of pharmaceutical care interventions on glycemic control and other health-related clinical outcomes in patients with type 2 diabetes.		
Study setting	Outpatient diabetes clinic		
Study design	Parallel randomized controlled trial		
Follow-up period	6 months		
Sample	N	106	
		Intervention	Control
	Sex (% male)	38.5	48.1
	Age (years ± SD)	52.9 ± 9.6	53.2 ± 11.2
	Baseline HbA1c (% ± SD)	8.9 ± 1.6	8.2 ± 1.3
	Comorbidities	Not reported	
Intervention			
Description	Assessment of patient condition. Compose care plan and discuss with physicians. Monitoring of lab results. During meeting with patient; structured patient education and counseling about DM2, medication, side effects, adherence to self-care activities. Also printed information material was provided containing the following information; medication, lifestyle modifications, self-care activities. During every visit to the clinic the patient had a 30 minute session with the pharmacist. Also telephone calls were made to discuss and review the care plan.		
Frequency of meetings	3 visits		
Duration of meetings	30 minutes per visit		
Intervention team	Pharmacist		
Education intervention team	Not reported		
Intervention topics	Diabetes education, medication, lifestyle, individual care plan/ goal setting, self-management skills, other		
Control group			
Description	Usual care provided by medical and nursing staff		
Outcomes			
Clinical outcomes	HbA1c, fasting blood glucose, lipid profile, weight, height, blood pressure		
Patient reported outcomes	Adherence (Morisky scale), self-care (SDSCA), diabetes knowledge (Michigan diabetes knowledge test)		

Appendix Table 3: Continued.

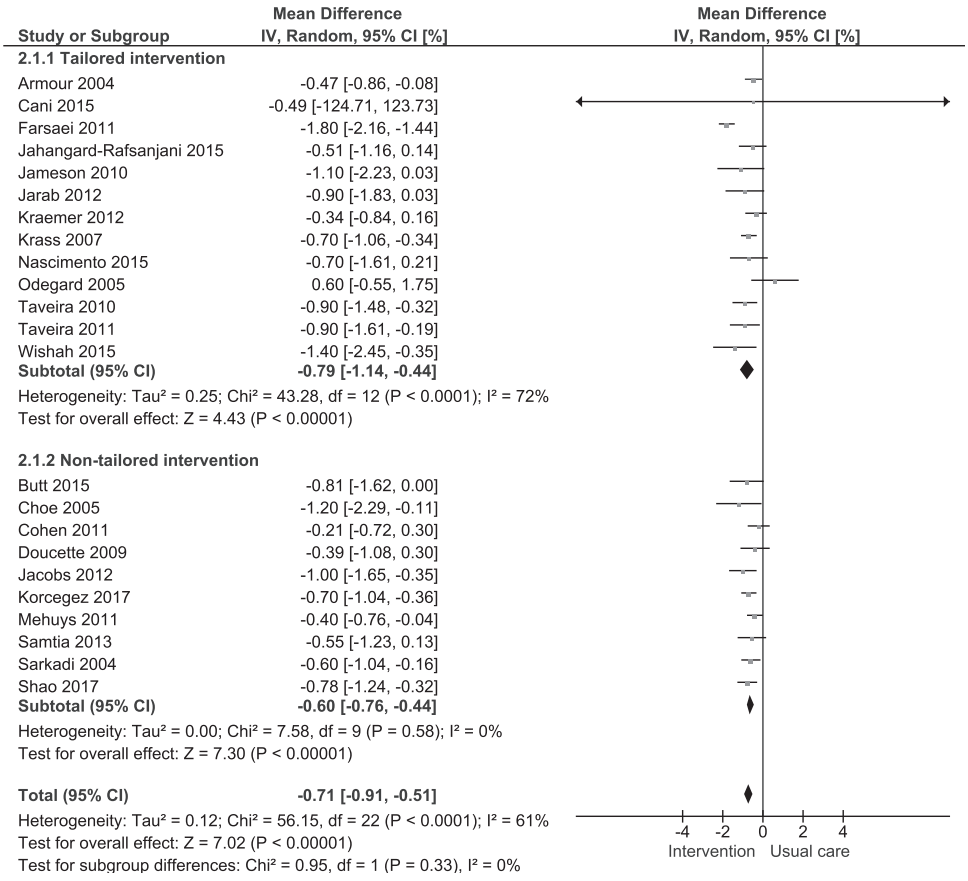
Results	
Clinical results	HbA1c: Statistical significant improvement in both intervention and control groups as well as between groups in favor of the intervention group. Fasting blood glucose: Improvement in both groups. Statistical significant difference between groups in favor of intervention group. Lipid profile: Significant improvement in intervention and control groups, but not between groups. BMI: No significant difference within and between groups.
Patient reported results	Adherence: Improvement in both intervention and control group. Statistical significant difference between groups in favor of intervention group. Self-care: Intervention group had statistical significant better scores compared to baseline and compared to control group after 6 months. Diabetes knowledge: At baseline both control and intervention group had insufficient knowledge. After 6 months statistical significant improvement in intervention group compared to control group.

Appendix Table 4: Exclusion reasons full text papers

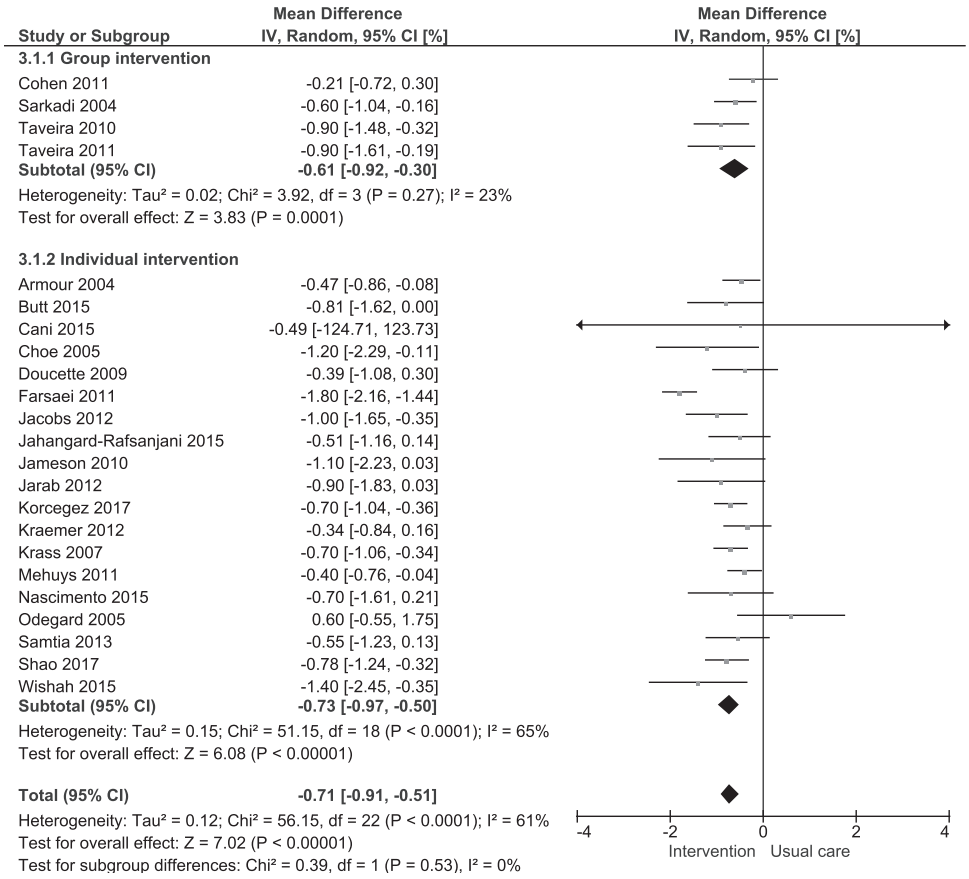
Author	Reason for exclusion
Adepu and Ari, 2010[25]	Not enough information to determine if study fulfilled inclusion criteria
Ahmad et al., 2015[26]	No self-management
Bindu Murali et al., 2016[27]	No ambulatory care setting
Borges et al., 2010[28]	No self-management
Buxton et al., 2010[29]	No peer reviewed research
Chan et al., 2012[30]	No self-management
Christie et al., 2014[31]	No peer reviewed research
Cohen et al., 2010[32]	No RCT
Colom, 2011[33]	Language; Spanish
Cranor and Christensen, 2003[34]	No RCT
Elasy et al., 2001[35]	Gestational diabetes
Erku et al., 2017[36]	No self-management
Farsaei et al., 2010[37]	Duplicate study
Fornos Perez et al., 2004[38]	Language; Spanish
Fornos et al., 2006[39]	No self-management
Hassaballa et al., 2015[40]	Pharmacist plays minor role in intervention
Iram et al., 2010[41]	Not enough information to determine if study fulfilled inclusion criteria
Jennings and McAdam Marx, 2012[42]	No peer reviewed research
Krass et al., 2011[43]	No usual care control group
Lyons et al., 2016[44]	No separate results for diabetes patients
MacLean et al., 2012[45]	Pharmacist plays minor role in intervention
Manju et al., 2016[46]	No self-management
Mitchell et al., 2011[47]	No RCT
Moore et al., 2013[48]	No RCT
Ndefo et al., 2017[49]	No RCT
Nielsen et al., 2006[50]	No RCT
Nishita et al., 2013[51]	Pharmacist plays minor role in intervention
Nor Elina et al., 2014[52]	No peer reviewed research
Obarcanin et al., 2015[53]	No self-management
Obreli et al., 2011[54]	No self-management
Obreli –Neto et al., 2011[55]	No self-management
Raji et al., 2002[56]	No self-management
Ramanath and Santhosh, 2011[57]	Not enough information to determine if study fulfilled inclusion criteria
Rothman et al., 2004[58]	No peer reviewed research
Sadur et al., 1999[59]	Pharmacist plays minor role in intervention
Shane-McWhorter et al., 2015[60]	No RCT
Shrader et al., 2013[61]	No RCT
Suppapitiporn et al., 2005[62]	Not enough information to determine if study fulfilled inclusion criteria
Taylor et al., 2003[63]	No self-management
Uehara et al., 2011[64]	Not enough information to determine if study fulfilled inclusion criteria

Search	Add to builder	Query	Items found	Time
#6	Add	Search ((((pharmacists[mesh] or pharmacy[mesh] or pharmacies[mesh] or pharmaceutical services[mesh] or pharmacists[tw] or pharmacist[tw] or pharmacy[tw] or pharmacies[tw] or pharmaceutical[tw]))) AND (((diabetes mellitus[mesh term]) OR (diabetes[tw] or dm[tw] or diabetic[tw])))) AND (((medication therapy management[mesh term] or self care[mesh term] or self efficacy[mesh term] or patient participation[mesh term] or medication adherence[mesh term] or medication compliance[mesh term] or patient compliance[mesh term])) OR (medication management[tw] or self management[tw] or self-management[tw] or self care[tw] or self-care[tw] or self efficacy[tw] or self-efficacy[tw] or patient participation[tw] or adherence[tw] or nonadherence[tw] or compliance[tw] or noncompliance[tw]))	1055	04:07:43
#5	Add	Search ((medication therapy management[mesh term] or self care[mesh term] or self efficacy[mesh term] or patient participation[mesh term] or medication adherence[mesh term] or medication compliance[mesh term] or patient compliance[mesh term])) OR (medication management[tw] or self management[tw] or self-management[tw] or self care[tw] or self-care[tw] or self efficacy[tw] or self-efficacy[tw] or patient participation[tw] or adherence[tw] or nonadherence[tw] or compliance[tw] or noncompliance[tw])	296998	03:44:50
#4	Add	Search ((diabetes mellitus[mesh term]) OR (diabetes[tw] or dm[tw] or diabetic[tw]))	529094	03:40:10
#1	Add	Search (pharmacists[mesh] or pharmacy[mesh] or pharmacies[mesh] or pharmaceutical services[mesh] or pharmacists[tw] or pharmacist[tw] or pharmacy[tw] or pharmacies[tw] or pharmaceutical[tw])	235914	03:38:11

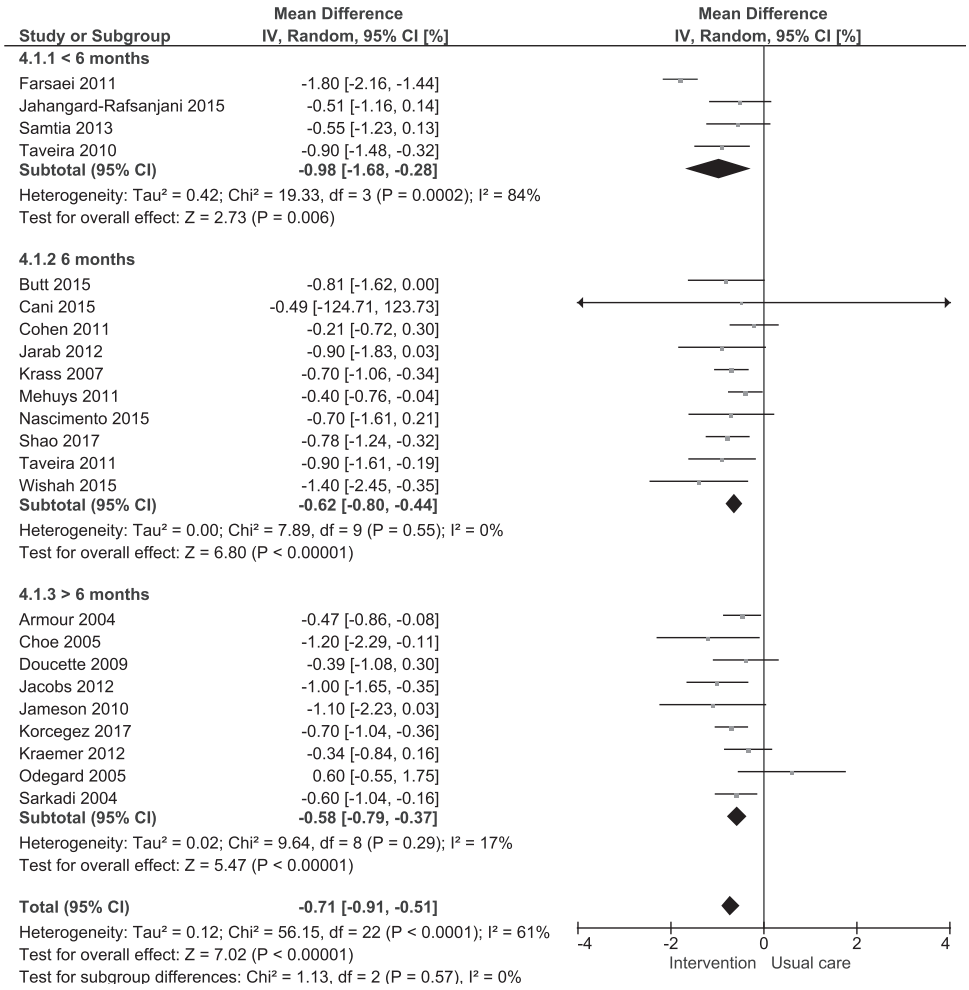
Appendix Figure 1: Search strategy PubMed



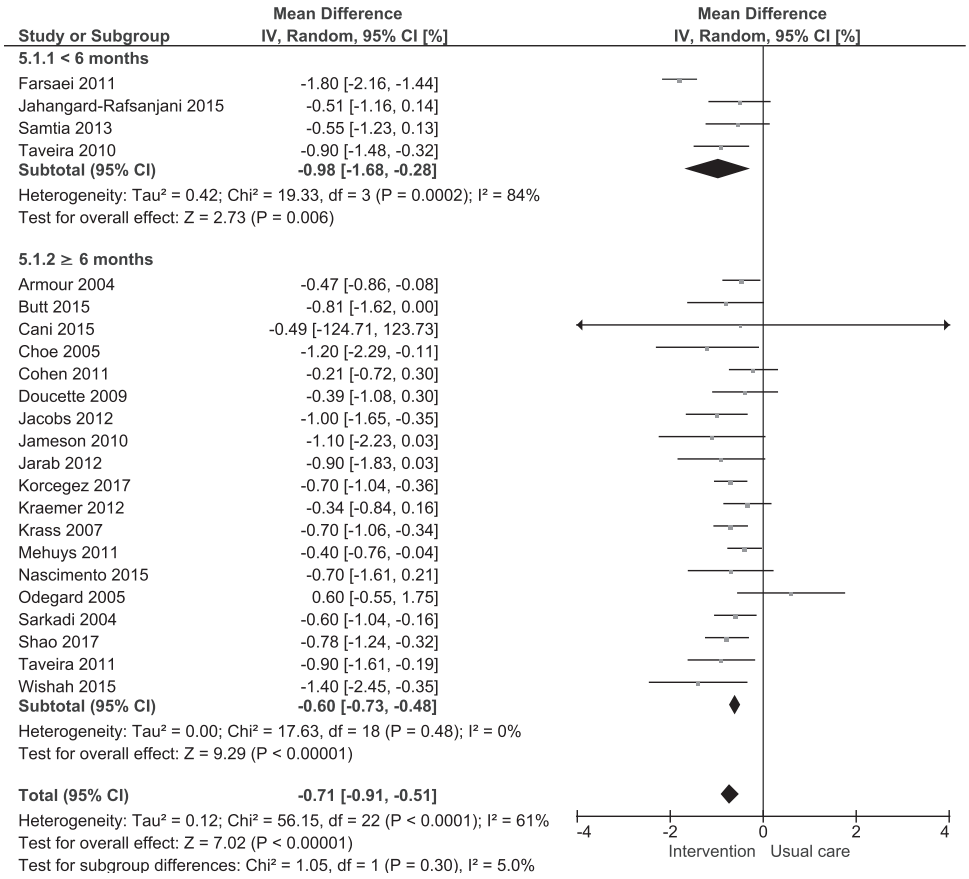
Appendix Figure 2A: Subgroup analysis tailored intervention



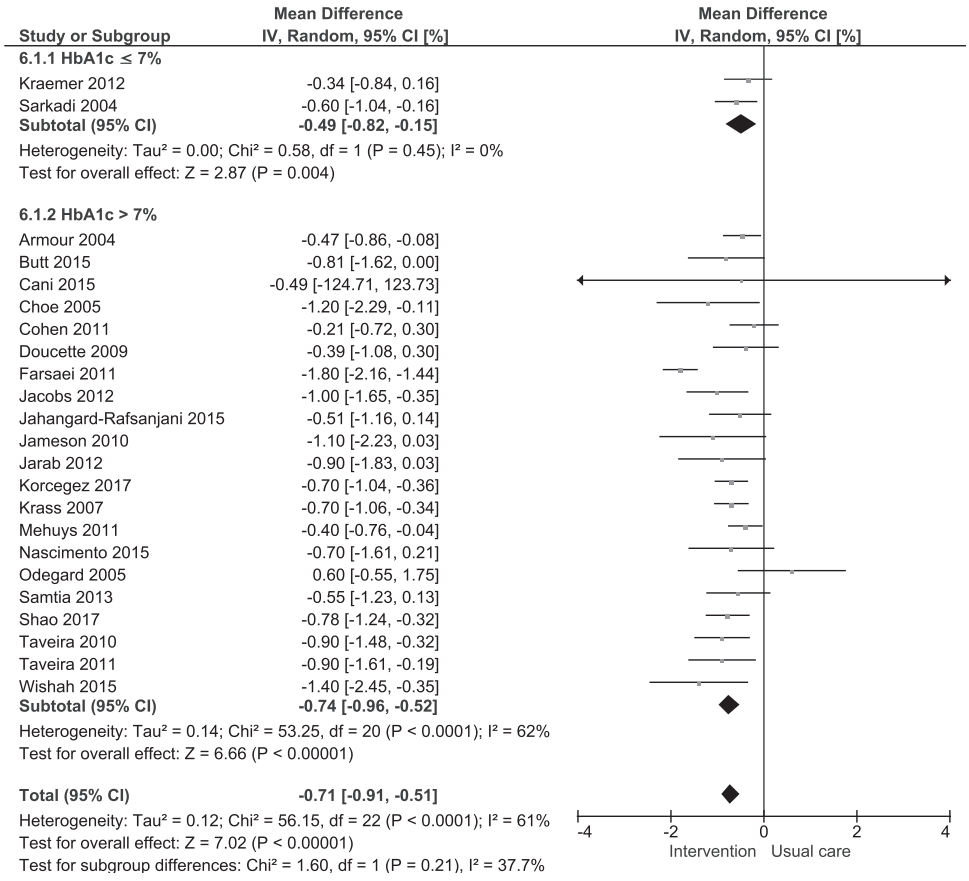
Appendix Figure 2B: Subgroup analysis group vs. individual intervention



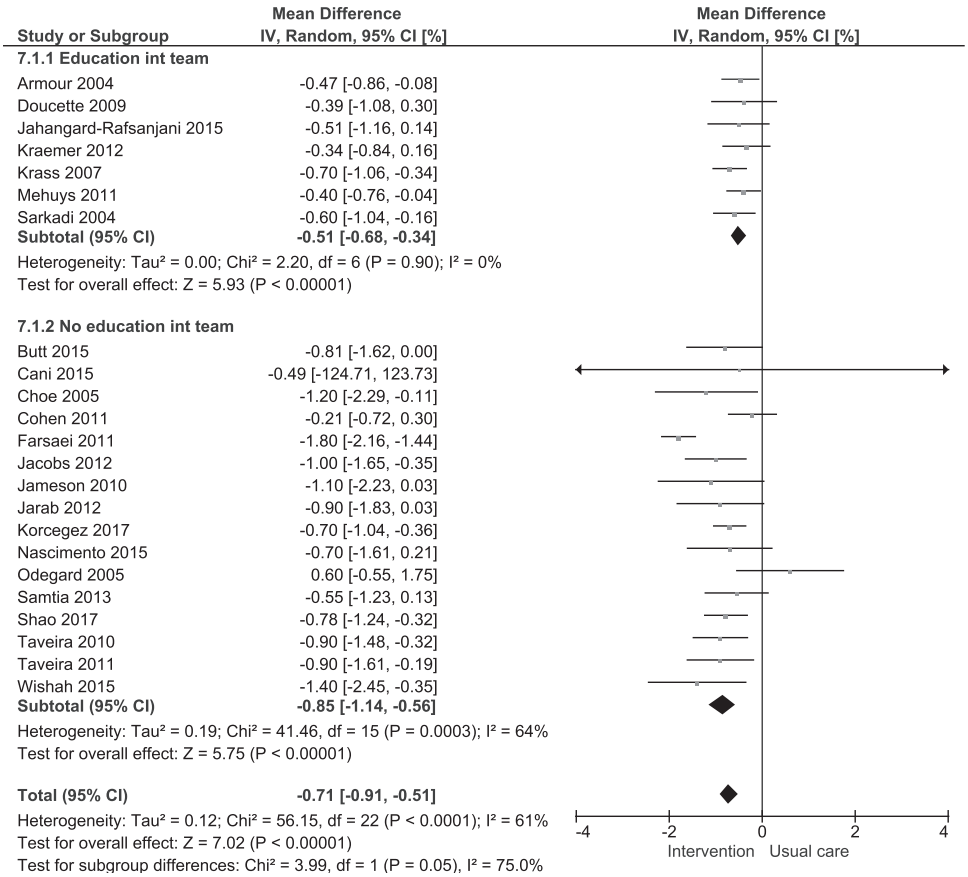
Appendix Figure 2C: Subgroup analysis <6, 6, >6 months follow-up



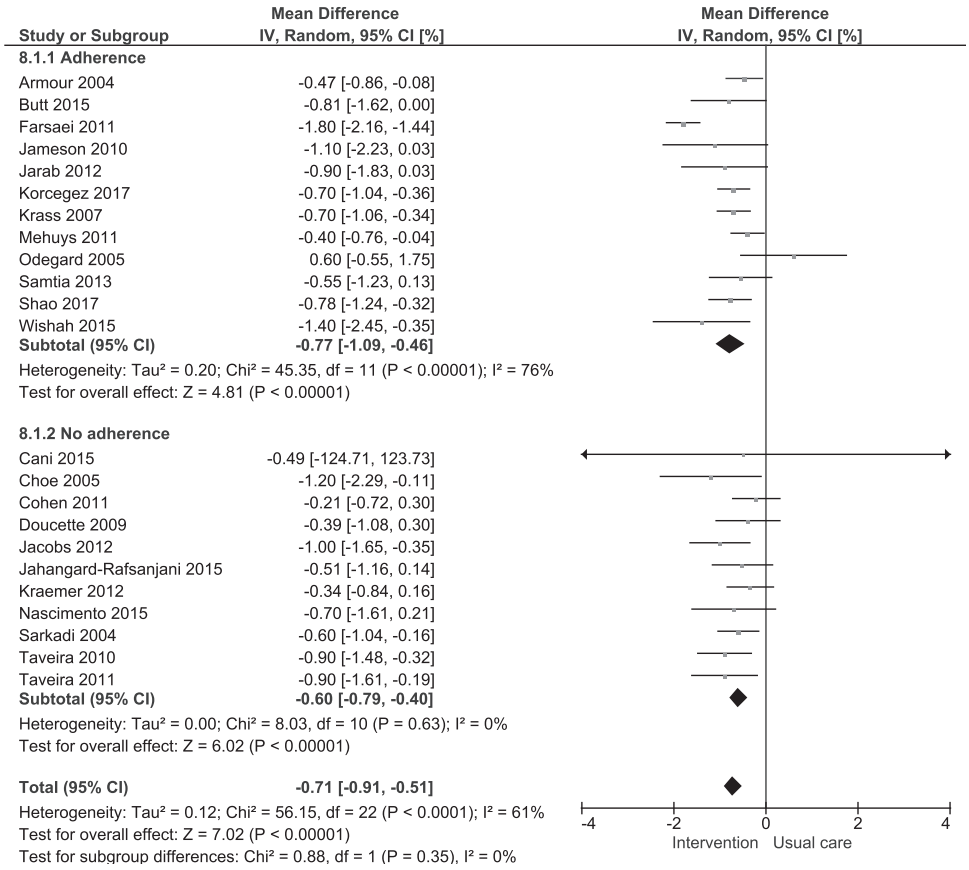
Appendix Figure 2D: Subgroup analysis <6 months vs. ≥ 6 months follow-up



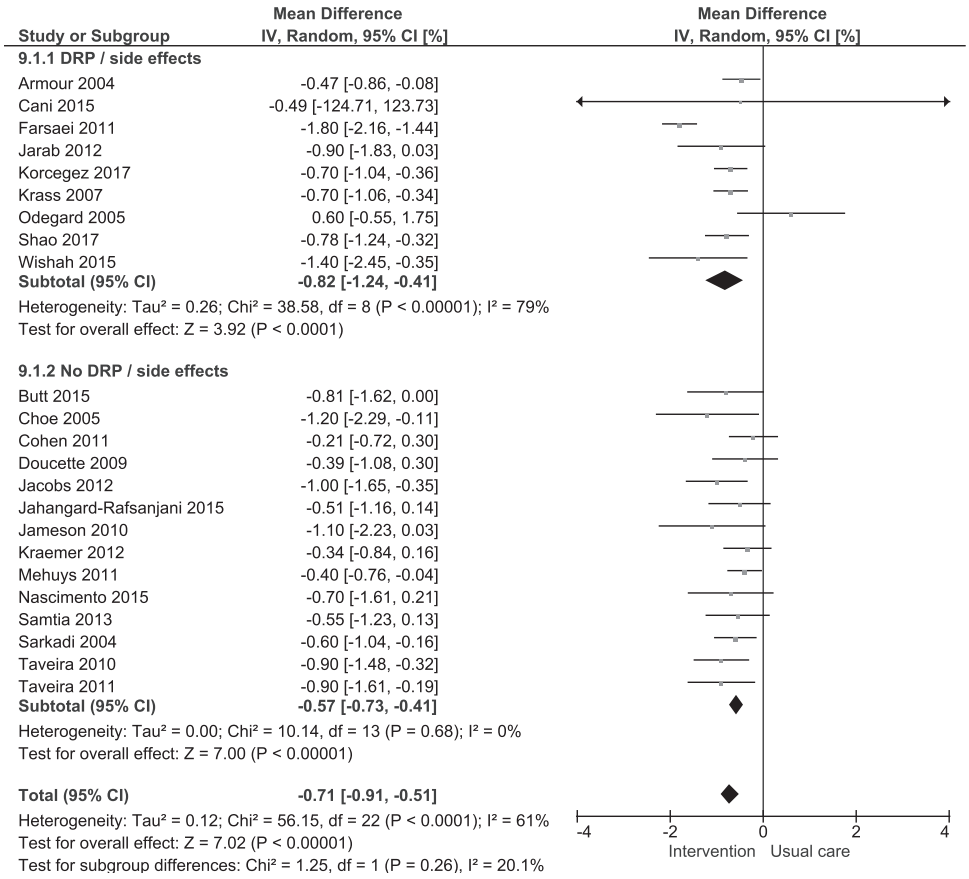
Appendix Figure 2E: Subgroup analysis baseline HbA1c cut-off 7%



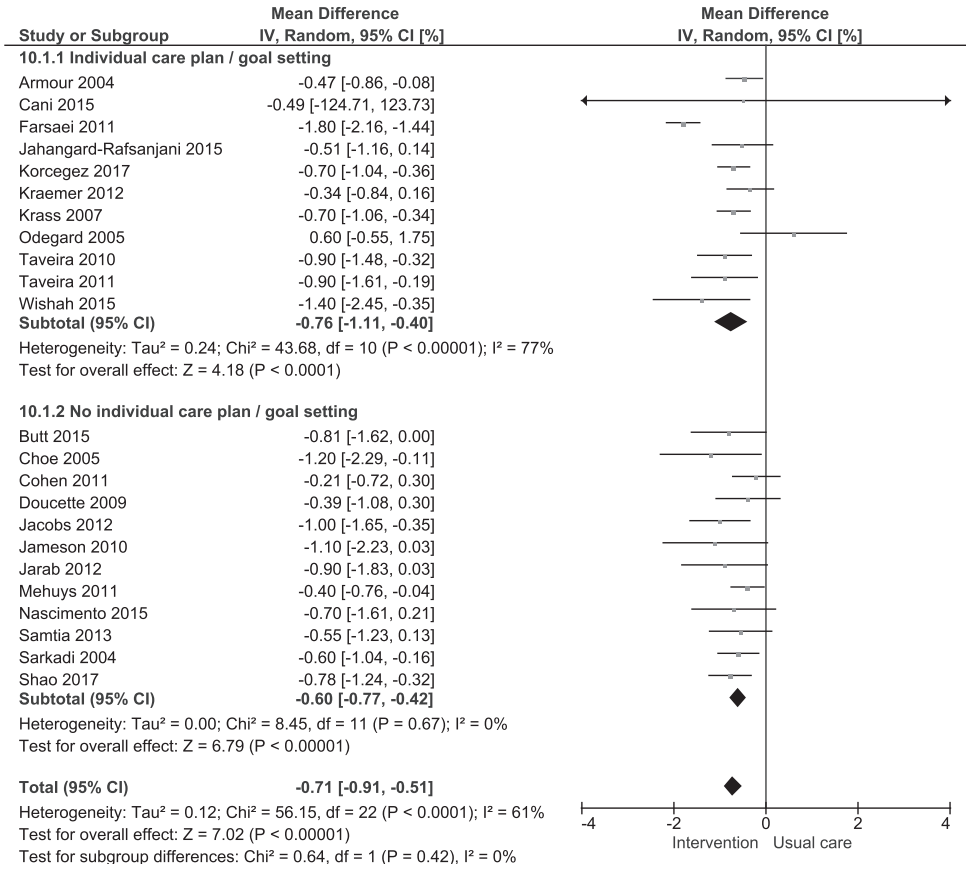
Appendix Figure 2F: Subgroup analysis education for intervention team



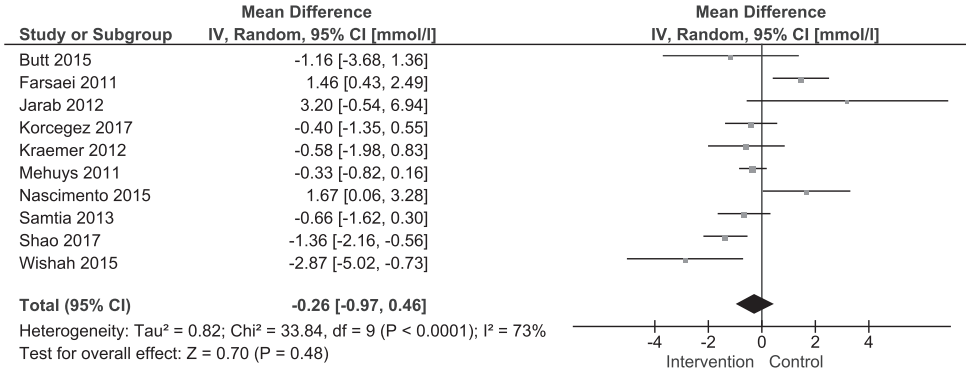
Appendix Figure 2G: Subgroup analysis adherence as intervention component



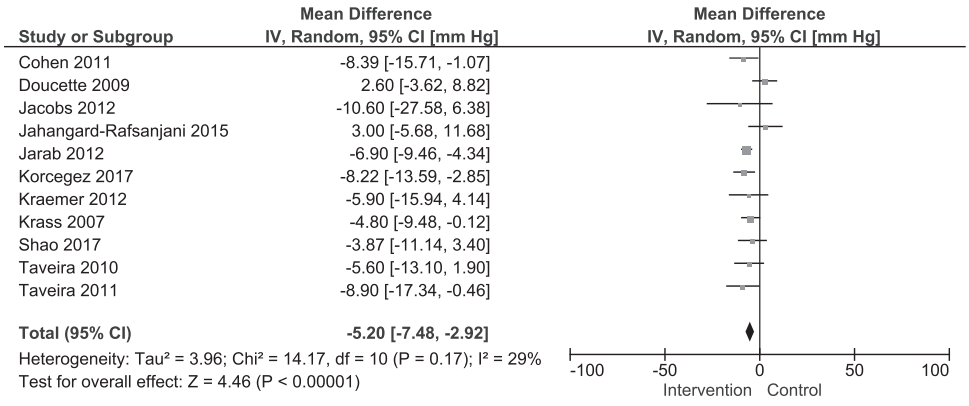
Appendix Figure 2H: Subgroup analysis DRP/ side effects as intervention component



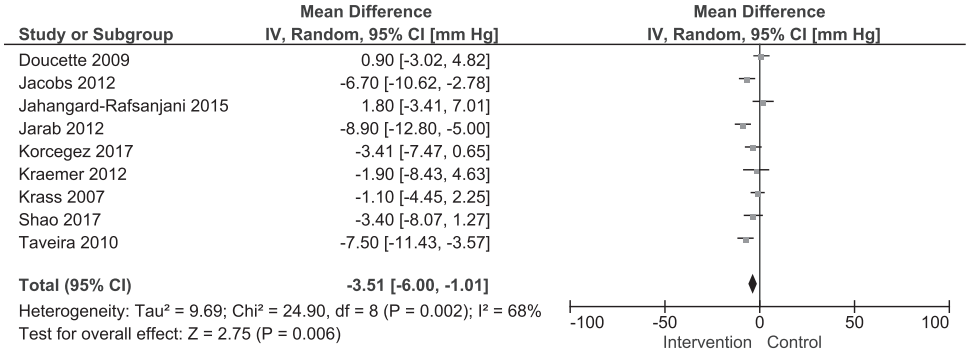
Appendix Figure 2I: Subgroup analysis individual care plan/ goal setting as intervention component



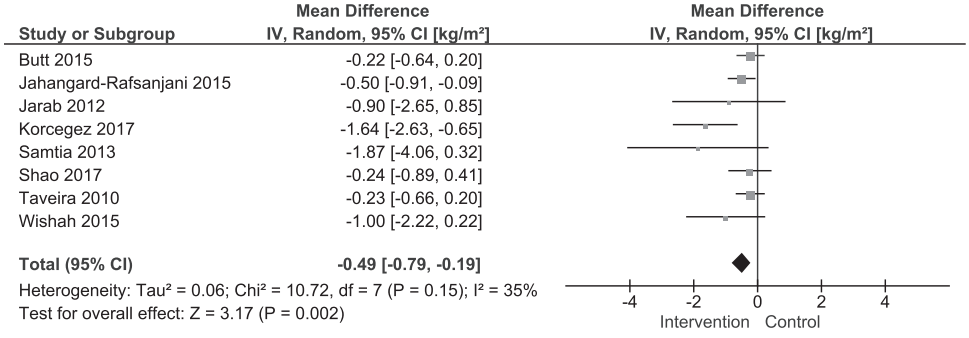
Appendix Figure 3: Pooled results "Blood Glucose"



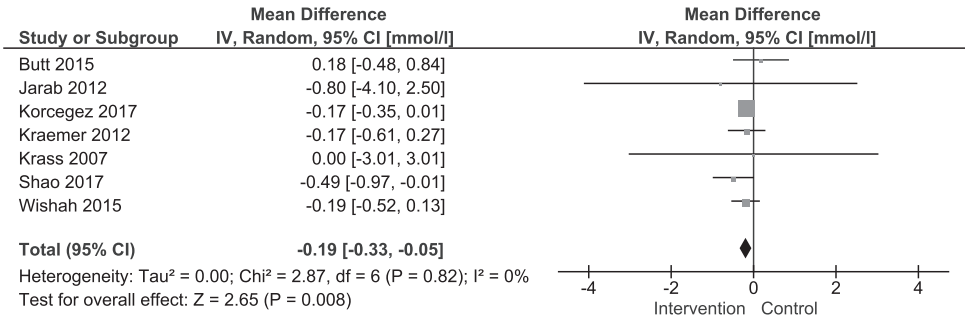
Appendix Figure 4A: Pooled results "Systolic Blood Pressure"



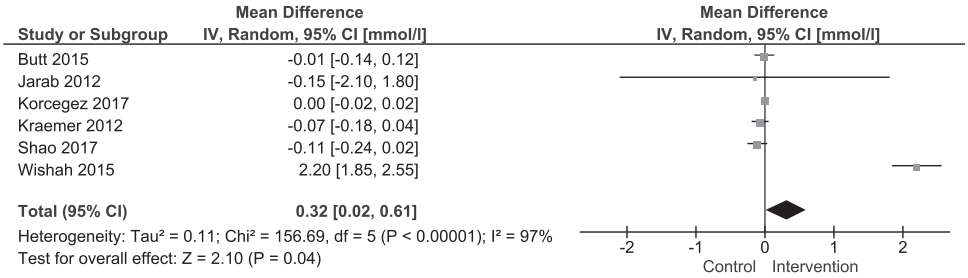
Appendix Figure 4B: Pooled results "Diastolic Blood Pressure"



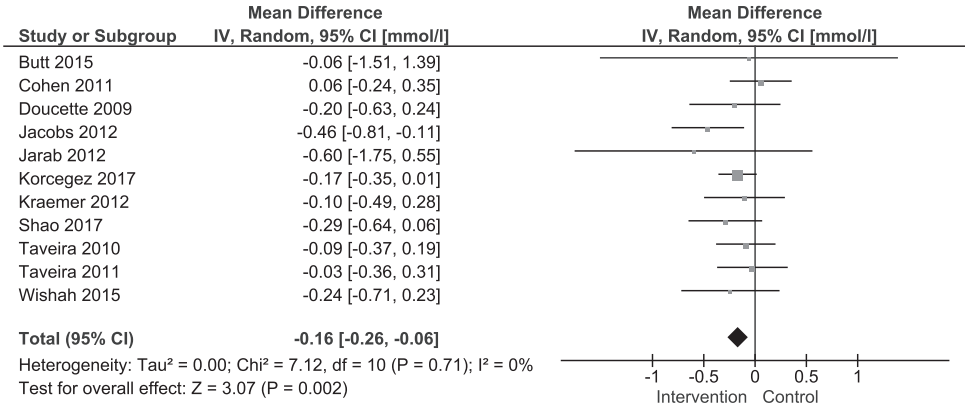
Appendix Figure 5: Pooled results "BMI"



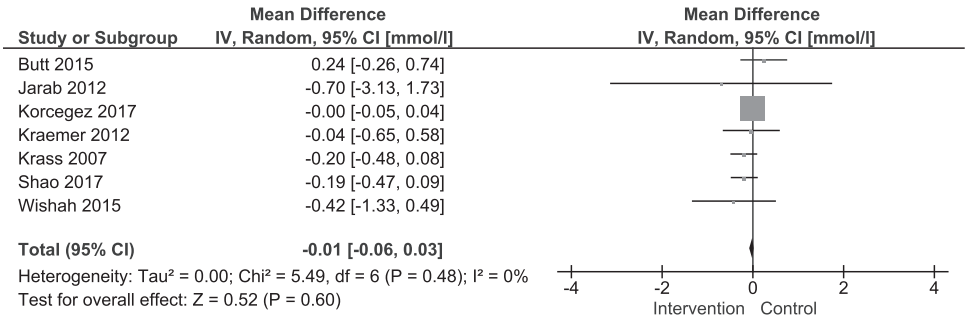
Appendix Figure 6A: Pooled results "Lipids – Total cholesterol"



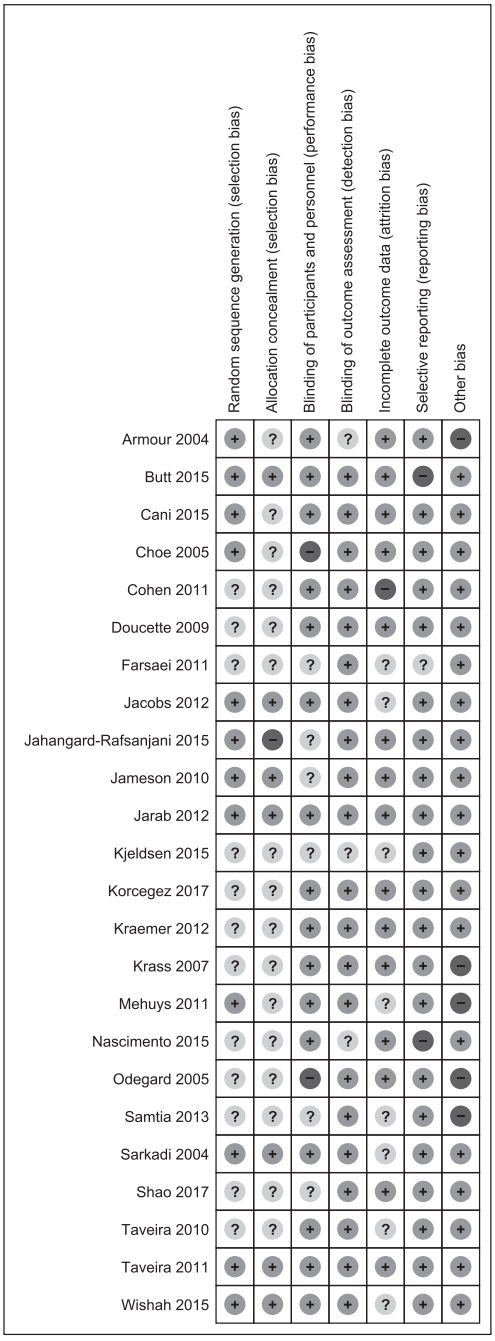
Appendix Figure 6B: Pooled results "Lipids – HDL-C"



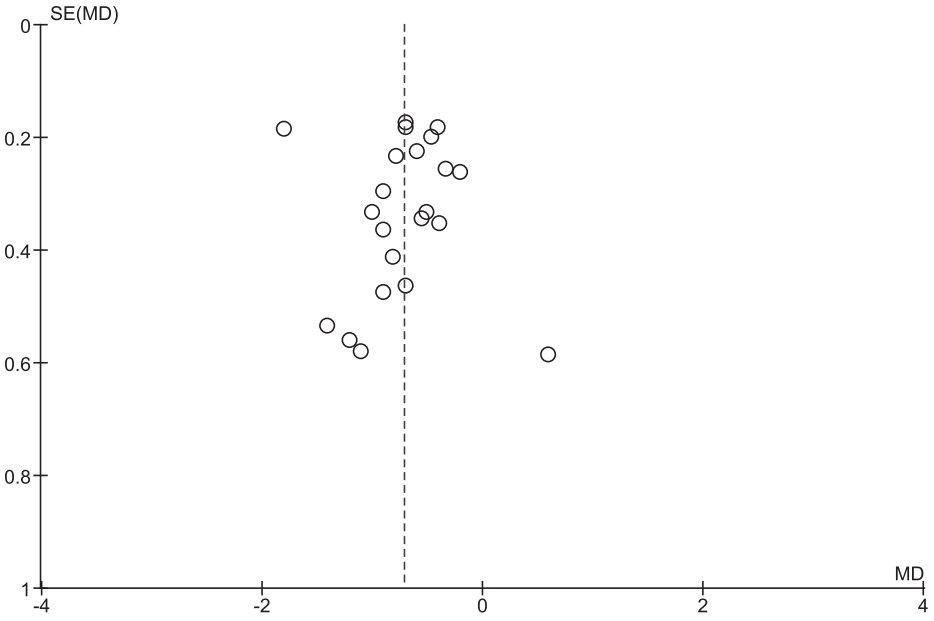
Appendix Figure 6C: Pooled results "Lipids – LDL-C"



Appendix Figure 6D: Pooled results "Lipids – Triglycerides"



Appendix Figure 7: Risk of Bias



Appendix Figure 8: Funnel Plot of Publication Bias (Cani et al., 2015(3) has been left out due to the extremely small SE).

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