Journal of
Diabetes Research & Clinical Metabolism
ISSN 2050-0866

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Research Open Access

Multiple pharmacological interventions targeting cardiovascular disease risk factors in individuals with type 2 diabetes-systematic review

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Abstract

Background: The use of pharmacological agents has been shown to slow down the progression of microvascular and macrovascular complications. Most clinical trials address one pharmacological intervention at a time. To date, only a few studies explored multi-factorial pharmacological interventions in T2DM individuals for preventing CVD related complications. Given the current therapeutic inertia in pharmacological management of CVD risk factors, it is important to establish the benefits of a more holistic approach. Therefore, the aim of this review is to assess the efficacy of multiple pharmacological interventions for cardiovascular diseases (CVD) risk factors with or without conventional care in reducing all cause mortality, CVD mortality, stroke and cardiovascular events among adults with type 2 diabetes. Current evidence fails to support the benefit of multiple pharmacological interventions on all cause mortality and death from cardiovascular causes. However, beneficial effects were seen on the reduction of the overall number of cardiovascular events and there were promising trends for secondary outcomes such as stroke, myocardial infarction, revascularisation and amputation.

Keywords: Cardiovascular risk factors, diabetes, mortality, pharmacological interventions, systematic review

Introduction

Around 300 million people worldwide have diabetes [1]. Moreover diabetes related deaths are projected to double between 2005 and 2030 [1,2]. Patients with type 2 diabetes mellitus (T2DM) are at risk of developing cardiovascular diseases (CVD) and other complications such as blindness, end stage renal impairment and lower limb amputations in some circumstances [3,4,5]. CVD is responsible for about 80% of the total mortality in individuals with T2DM, contributing substantially to direct health care costs and decreased quality of life [6,7,8].

Interventions targeted at preventing CVD onset for high risk individuals with T2DM can delay or reduce the progression of complications related with diabetes [9,10,11]. In addition, CVD prevention programs used in several countries have led to reduction in diabetes-related complications [10,11,12]. These programs were aimed at diet modification, promotion of physical activity, weight loss, smoking cessation, educational counselling and/or pharmacological interventions. Moreover, several studies have addressed several combinations of the above mentioned interventions [12,13,14].

The United Kingdom Prospective Diabetes Study (UKPDS) identified several important CVD risk factors in individuals with T2DM including hyperglycaemia, hypertension and dyslipidaemia [15,16,17]. Comprehensive management of glucose, blood pressure and lipid levels is essential to the provision of best care to individuals with T2DM [16,17,18].

The use of pharmacological agents in addition to lifestyle modification has been shown to slow down the progression of microvascular and macrovascular complications [19,20,21,22]. Most clinical trials address one pharmacological intervention at a time in addition to lifestyle modifications [23-30]. To date, only a few studies explored multi-factorial pharmacological interventions in T2DM individuals for preventing CVD related complications. Most of these studies were a cohort design, and more accurately evaluated the efficacy or effectiveness of CVD risk management programs incorporating single pharmacological strategies [31,34]. Given the current therapeutic inertia in pharmacological management of CVD risk factors, it is important to establish the benefits of a more holistic approach. The current proposed systematic review will only focus on RCTs designed to evaluate the specific effect of multiple pharmacological interventions (with or without lifestyle modifications) to optimise management of CVD risk factors on cardiovascular outcomes and mortality in patients with type 2 diabetes.

Objectives

To assess the efficacy of multiple pharmacological interventions (with or without lifestyle modifications)

to optimise management of multiple CVD risk factors on cardiovascular outcomes and mortality in patients with type 2 diabetes.

Search and study selection

Ovid MEDLINE® (1948 to present with daily update), Cochrane Central Register of Controlled Trials (4th Quarter 2010) and Embase were searched for papers dating from 1995 to February 2012: this timeframe was chosen because the landmark publications for clinical trials demonstrating cardiovascular benefits of statins began being published from 1994 [35,36]. Clinical trials for key weight loss therapies such as orlistat and sibutramine also emerged after this period. We used the relevant diagnostic terms (*e.g.* cardiovascular disease, stroke, coronary disease, mortality, and diabetes mellitus type II), together with text word searches for specific interventions (*e.g.* antihypertensives, blood pressure control, hypolipidemic agents, lipid-lowering therapy, weight management, smoking cessation, aspirin, anticoagulants). Text word searches using the terms "multiple", "multifaceted" and "multifactorial" were applied. Specific interventions of interest were searched including antihypertensive management, smoking cessation, lipid lowering drugs management, aspirin, antiplatelet, anticlotting factors and obesity drugs. Disease terms such as diabetes, type 2 diabetes and diabetes mellitus were also used as shown in **Appendix 1**. This was supplemented by examining the reference lists of each Randomised Controlled Trial (RCT) study identified. We limited the review to English language articles. Authors were also contacted for the raw data if it was not stated in the paper.

The original search titles and abstracts obtained through searches were checked independently by two reviewers (HK and YP). Each paper thought to be of possible relevance was obtained and read by all three reviewers (HK, KM and YP) independently to determine whether it fitted specified inclusion criteria. Disagreements were discussed and resolved between the three reviewers.

Inclusion and exclusion criteria

RCTs identified for the primary or secondary prevention of CVD in patients with type 2 diabetes by means of multiple risk factor pharmacological interventions were included in the review (*i.e.* separate pharmacological intervention strategies for two or more CVD risk factors such as blood pressure reduction, lipid management, antiplatelet therapy, smoking cessation and weight reduction, excluding glycaemic control). Comparators are defined as conventional care. They could be with or without non-pharmacological treatments (such as counselling or education, behavioural interventions). Trials aimed at patients with any stage of their diabetes and located in middle- to high-income countries were included. Children under 18 and of duration less than six months were excluded.

Outcomes of interest

The primary outcome of interest was reduction in mortality in a head to head comparison. The secondary outcome of interest was a reduction in the total number of cardiovascular events. Other outcomes such as stroke, myocardial infarction, revascularisation, amputation or other cardiovascular related events reported as a first cardiovascular event were also included.

Quality control

Relevant data were extracted from each study as shown in **Table 1**. Information such as author, publication year, trial duration, number of patients in the study, patients' age, description of the intervention, findings and authors' conclusion were collected. Full paper assessments for quality were completed independently by two reviewers (HK and KM). Data extraction was undertaken by HK and reviewed by the other researchers [38,39].

The methodological quality of the studies that met the inclusion criteria was assessed using the components of the study design most closely aligned to internal validity as suggested by the Cochrane Collaboration [38]. These components include: adequate description of randomisation, blinding of patients and outcome assessors and adequate description of follow up and withdrawals.

Statistical analysis

A meta-analysis was performed only on the results extracted from three studies. We analysed the data using the standardised data extraction tool from the Revman v.5 package and all results were presented with a 95% confidence Interval (CI) [38,39]. We compared dichotomous data using Risk Ratio (RR). Heterogeneity, (I2) which describes the proportion of total variation in study estimates that is due to variability, was assessed using the standard chi-squared. Study data was considered heterogeneous if I2 statistic was >50%. For the forest plot, we used the random effect method due to the variability of the participants (newly diagnosed versus patients with past diagnosed diabetes) in all three studies [38].

Results

We found a total of 64 potentially relevant citations from Medline, Embase, Cochrane trials register and hand searches. After removal of all duplicates, 48 reporting clinical data were retained. Only ten addressed the impact of multiple pharmacological interventions on CVD risk factors in type 2 diabetes (**Figure 1**) [41-50].

Seven of these ten trials were excluded because they did not address the outcomes of interest. Details of the remaining three studies are summarized in **Table 1**. In general, all studies compared an intervention group allocated to multi-drug therapy such as anti-hypertensive and hypolipidaemic therapy commonly, and occasionally aspirin in addition to the other two treatments-versus a

Table 1. Multiple risk factor intervention trials.

Study	Sample	Sample size, mean age at baseline	Intervention	Outcomes measured	Duration of follow up	Finding
Gaede et al., 2008 (Steno-2 study)[47]	Patients with type 2 diabetes and persistent microalbuminuria	160 patients, (55.1 ± 7.2).	All patients in the intensive treatment group were prescribed blockers of the renin angiotension system regardless of blood pressure and received low dose aspirin as primary prevention. Behaviour modification and a stepwise pharmacological therapy for blood pressure, dyslipidaemia and hyperglycaemia were also overseen by a project team (doctor, nurse and dietitian). The intensive therapy group were treated at a specialist diabetes centre and had defined targets consistent with the latest guidelines of the American Diabetes Association. The control group received conventional treatment for multiple risk factors from their general practitioner, according to the 1988 recommendations of the Danish Medical Association (which did not include intensive pharmacological therapy)	Cardiovascular events, including death from cardiovascular causes, non fatal stroke, non fatal myocardial infarction, coronary artery bypass grafting (CABG), percutaneous coronary intervention (PCI), revascularization for peripheral atherosclerotic disease and amputation.	The mean treatment period was 7.8 years. Patients were subsequently followed observationally for a mean of 5.5 years. The primary end point at 13.3 years of follow up was the time to death from any cause.	Intensive intervention with multiple drug combinations and behaviour modification had beneficial effects on cardiovascular complications and rates of death from any cause. The rate of death among patients in the conventional group was 50% compared with 30% in the intensive treatment group which indicates poor prognosis for patients in the absence of intensive treatment.
Joss et al., 2004[50]	Patients with type 2 diabetes and nephropathy	90 patients (63 ± 7)	The intensive treatment group was introduced in steps starting with blood pressure and cholesterol management followed by dietary intervention. The control group had conventional management.	Clinical/Biochemical factors such as BP, HbA1c, lipids and BMI were measured. Cardiovascular events such as death, amputation or heart failure were reported. The rate of progression of renal disease in the second year of follow up was also measured.	2 years	Significant improvement in BP, lipids and creatinine clearances were seen in the intensive treatment. The number of cardiovascular events in the intensive treatment was significantly lower than the control group.
Griffen et al., 2011 (ADDITION-Europe) study[37]	Screen-detected patients with type 2 diabetes	3055 patients (60.3±6.9)	The protocol is characterised by intensive treatment of glucose, blood pressure and lipids and structured lifestyle education (dietary modification, weight loss, increased physical activity, smoking cessation and improving adherence to medication). The intensive therapy group had defined targets for each treatment unlike the control group patients who received usual care.	Clinical/Biochemical parameters were collected such as BP, HbA1c and lipids. The primary endpoint was a composite of first cardiovascular event, including mortality, morbidity, revascularisation and amputation. The secondary endpoints were the individual components of the primary endpoint and all-cause mortality.	5.3 years	Improvements in cardiovascular risk factors were slightly but significantly better in the intensive group. The incidence of first cardiovascular event was 7.2%in the intensive group and 8.5% in the routine care group and of all cause mortality 6.2% and 6.7% respectively.

control group. Counselling and/or behavioural intervention were also provided described in both groups of the studies included in the review as shown in **Appendix 2**. The three trials had 3305 patients in total with type 2 diabetes. Patients' ages ranged from 7-70 years. Duration of follow up ranged from 2 to 13.3 years.

Primary outcomes: mortality and morbidity

All three trials reported positive changes in clinical parameters as well as biochemical variables in favour of the intervention group. However not all trials described details of mortality rates (**Figure 2**, **Appendix 3**).

All cause mortality

A lack of evidence exists to support a reduction of death from any cause was observed in favour of the intervention group with a RR of 0.77 [95% CI, 0.50 – 1.18].

Death from cardiovascular cause

There is a lack of evidence to suggest a significant risk reduction of death from CVD which favoured the multifactorial pharmacological intervention; RR =0.71 [95% CI, 0.40 –1.26].

 doi: 10.7243/2050-0866-2-9

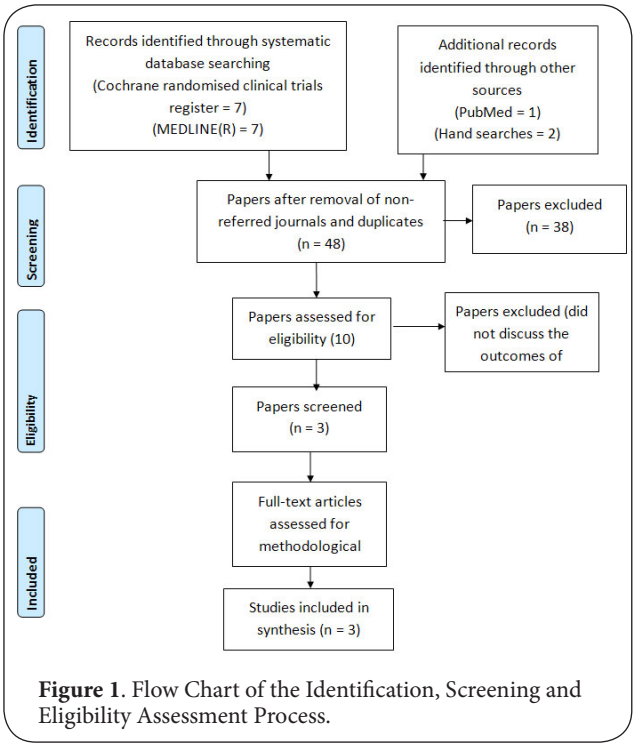

Figure 1. Flow Chart of the Identification, Screening and Eligibility Assessment Process.

Figure 2. All measured outcomes.

Outcome	Studies	Participants	Statistical method	Effect Estimate
All cause mortality	3	3260	Risk Ratio (M-H, Random, 95%CI)	0.77 [0.50, 1.18]
Death from cardiovascular causes	3	3260	Risk Ratio (M-H, Random, 95%CI)	0.71 [0.40, 1.26]
Non-fatal Myocardial Infarction	3	3260	Risk Ratio (M-H, Random, 95%CI)	0.68 [0.45, 1.05]
Non-fatal stroke	3	3260	Risk Ratio (M-H, Random, 95%CI)	0.58 [0.24, 1.38]
Amputation/ Revascularisation	3	3260	Risk Ratio (M-H, Random, 95%CI)	0.76 [0.52, 1.09]
Total cardiovascular events	3	3260	Risk Ratio (M-H, Random, 95%CI)	0.63 [0.43, 0.94]

Secondary outcomes

Number of total cardiovascular events

All three trials reported on the total number of individuals experiencing events during follow up. They demonstrated a significant reduction in the total number of events in favour of the intervention group; RR=0.63 [95% CI, 0.43 – 0.94].

Myocardial infarction (MI)

The combined trial results indicate a non-significant reduction of MI risk in favour of the intervention group with a RR of 0.68 [95% CI, 0.45 – 1.05].

Revascularisation and amputation

The included studies reported on revascularisation/amputation as a combined outcome, and the reduction in the combined risk of amputation or/ revascularisation observed in favour of the intervention group was not significant, with a RR of 0.76 [95% CI, 0.52 – 1.09].

Stroke

A lack of evidence exists in favour of the intervention group with a RR of 0.58 [95% CI, 0.24 – 1.38] to support a reduction of stroke.

Publication bias

We explored publication bias for all outcomes using a funnel plot. Visual inspection suggested symmetry for the primary and secondary outcomes, indicating no publication bias.

Methodological quality of included trials

We collected data for four methodological features of the identified studies and they were:

1. Allocation concealment
2. Randomisation
3. Double blinding
4. Outcome assessment

Allocation concealment means that the participant and others directly involved in treatment do not know to which treatment group the participant had been allocated. Randomisation ensured an equal chance of receiving the possible treatment. Double-blinding means that neither the participant nor the outcome assessor was aware of the identity of the treatment.

All three studies had a low risk of bias based on the above methodological features. In all included studies, Allocation to treatment groups was concealed and randomisation was done by an independent person such as a statistician or a computer. Double blinding was not employed in all three studies due to the nature of the interventions.

Discussion

Multi-factorial intervention of the cardiovascular risk factors is widely recognised as effective in the successful management of patients with type 2 diabetes.

This meta-analysis of three randomised controlled trials employing intensive pharmacological intervention for CVD risk factors demonstrated a non-significant reduction in the likelihood of death from any cause and risk of cardiovascular events such as myocardial infarction, stroke, amputation and revascularisation. There was, however, a significant reduction in the total number of cardiovascular events in favour of the intensive pharmacological CVD intervention group. These results could be attributed to either the additional behavioural interventions described in the included studies or the actual intensive pharmacological treatment given to the participants. Behavioural interventions are known to influence adherence to medications [13,14,51]. This

study also confirms the relative absence of trials examining endpoints for this important topic. We believe this to be the first comprehensive meta-analysis of this topic and hence will serve as a valuable overview of current evidence for clinicians and researchers.

Only three studies fulfilled our inclusion criteria of the review as shown in. All three studies reported on improvement in clinical and biochemical parameters in favour of the intervention groups. Differences in the risk ratio for all components of the primary and secondary outcomes favoured the intensive intervention groups. Differences in risk reduction were greatest for the total cardiovascular events and smallest for all cause mortality.

The large confidence intervals obtained for the primary outcome suggests that there is lack of evidence to suggest improvements in these outcomes. As for the secondary outcomes, significant risk reduction was only observed in the total number of cardiovascular events, in favour of the intervention group.

The lack of significance benefit observed in our study could be also attributed to several reasons such as; health professional adherence to treatments algorithms, medication/ lifestyle adherence by patients, the timing and nature of drugs prescribed, and the use of specific drug combinations. Another important factor to consider is the method of randomisation described in the studies was vastly different; cluster randomisation of the general practices rather than the individuals was used in the Addition-Europe study to achieve high participants' retention.

The diversity of study designs and populations, the complex nature of the intervention itself and the lack of studies addressing our aims such as a reduction in mortality and morbidity precluded a significant number of studies to be included in our current review. The patients with diabetes involved in the three studies were a combination of newly diagnosed as well as patients with existing diabetes and with either microalbuminurea or nephropathy. The types of interventions also varied between the studies. The results of this review also highlight the lack of studies addressing the various populations and the multiple treatment algorithms. Newly diagnosed diabetes may differ in their response to CVD multifactorial pharmacological interventions from those who have been diagnosed for several years.

It is worth pointing out that it is not common practice but it is acceptable to combine results from cluster RCTs to non-cluster RCTs in the same analysis depending on the clinical/practical reasons. Given the large number of participants included in the cluster RCT by Griffen *et al.,* 2011 and the use of raw numbers of participants in our analysis, it was deemed appropriate to combine the studies in our meta-analysis.

Statistical and clinical heterogeneity in our analysis presented some difficulties, particularly for multifactorial interventions due to the variation in population sampled and to the nature and context of the interventions. The potential effect of setting should also be considered as a possible explanation for heterogeneous results. Delivery of the ADDITION intervention was in primary care and largely by doctors and nurses; conversely, the other two trials involved multidisciplinary teams in specialist centres. As the number of studies addressing the efficacy of such interventions increase, a better picture will emerge on the overall efficacy of these interventions in the various populations.

It is possible that benefits cannot be detected in the early stages but emerge over time. This was clearly a potential factor preventing demonstration of significant benefit in the ADDITION-Europe primary endpoints. Lower than expected CVD incidence rates might well have contributed to the observation of non-significant differences to CVD endpoints, albeit in favour of the intensive intervention group [**35**]. Survival curves suggest benefits were only emerging at four years overall, although significant benefits from intensive treatment were demonstrated for the older (higher risk) subgroup. In addition, small but significant improvements to CVD risk factors had been demonstrated to suggest potential longer-term benefits. Longer follow up of patients involved will test whether intensive multifactorial treatment reduced cardiovascular risk in the long term as seen in the UKPDS. The current emphasis on early diagnosis, diabetes education and the availability of a wide range of therapeutic regimens with safer side effect profile make it easier to achieve good glycaemic control and control of CVD risk factors in patients with type 2 diabetes using intensified multifactorial regimes. However, therapeutic inertia and poor control of key CVD risk factors for patients with diabetes remain across most settings internationally. Our findings are important as a means of highlighting to health professionals the potential long-term benefits of early and holistic approaches to disease state management in diabetes. Considering the differences in outcomes between different interventions however, this benefit may be greater for patients with complications from diabetes, and when the intervention is delivered in well-resourced settings. Factors that need to be considered include the cost of treatment as these patients are taking multiple medications for their CVD risk factors, the effect of more complex medication regimens on patient adherence, and the availability of resources such as regular medical care and updated clinical practice guidelines to implement multifactorial pharmacological intervention for CVD risk factors in patient with type 2 diabetes. If approved for use, the much-anticipated 'polypill', combining aspirin with antihypertensive and lipid-modifying agents into a single pill, may assist with cost and lipid lowering drugs issues associated with more complex medication regimes.

The limitations of our results lie in the small number of studies included in this review. The three trials also have slightly different patient groups and interventions. Programs involving multiple CVD risk factor pharmacological

management is likely to be effective but there are a number of possible treatment algorithms not tested, the detail around counselling is poorly defined and therefore difficult to reliably replicate in practice and we cannot differentiate the drug vs. counselling benefit very well. Furthermore, our search strategy focussed on identifying trials with a clear pharmacological focus. It did not include trials where the intervention was primarily concerned with health professional behaviour change.

Implications for research

The current systematic review highlights the shortcomings in the published trials of multi-factorial pharmacological intervention in patients with type 2 diabetes. There is a lack of such studies across different populations and settings with a large number of participants that are powered enough to detect a change on mortality. There is also a need for long-term follow up of trials addressing mortality and morbidity among patients with newly diagnosed diabetes, to confirm the benefits of early intensive treatment. Most of the trials report on biochemical and clinical parameters. More research is needed to address this very gap in the literature.

Research on the effects and costs of health protection and CVD risk prevention would be of direct policy relevance. Furthermore, qualitative studies examining how participants perceive and respond to the advice and treatment given in these randomised controlled trials could be very helpful in shaping future interventions and clinical guidelines.

Additional files

Appendix 1
Appendix 2
Appendix 3

Competing interests

The authors declare that they have no competing interests.

Publication history

Received: 09-Nov-2012 Revised: 29-Jan-2013
Accepted: 04-Feb-2013 Published: 21-Feb-2013

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Citation:
Khalil H, Namara K M and Y P: **Multiple pharmacological interventions targeting cardiovascular disease risk factors in individuals with type 2 diabetes-systematic review**. *Journal of Diabetes Research and Clinical Metabolism* 2013, **2**:9.
http://dx.doi.org/10.7243/2050-0866-2-9