Pharmacological Interventions for Prevention of Cardiovascular Disease in Type 2 Diabetes (T2DM): A Review of Some Meta-analytic Comparisons

Anthony Shannon*, Ching Wong

Warrane College, The University of New South Wales,
KvB Institute of Technology, North Sydney, NSW 2060, Australia
E-mil: tony@warrane.unsw.edu.au
*Corresponding author

Abstract: The purpose of the studies reported here was to examine the effects of pharmacological interventions in the prevention or reduction of the risk of cardiovascular disease in Type 2 diabetes mellitus (T2DM). The original studies were from the results of meta-analyses of experimental data. This paper reviews these studies in order to comment on apparent anomalies among their results.

Keywords: Diabetes mellitus, Meta-analysis, Glycaemic control, Lipids, Blood pressure.

Introduction

There is a lack of consistent evidence in the literature about the prevention and treatment of macro-vascular disease in Type 2 diabetes (T2DM), this being one of the many potential complications associated with having the disease. Intuitively one knows that blood pressure and cholesterol levels have to be controlled, but how best to do this, either in general or for particular classes of patients?

Meta-analyses of the literature have been carried out but even they do not convey an unequivocal picture of appropriate procedures. This paper is an attempt to get an overall perspective of what works in general, based upon studies considered by other authors in previous meta-analyses. Follow up is required then for specific treatments as detailed in the references.

We note that in some of the studies cited in previous meta-analyses:
- some studies mixed up Type 1 (T1DM) and T2DM in the one study;
- the methods of defining patients with diabetes mellitus (DM) varied;
- some studies were confined to one gender;
- the total numbers in some studies were not reported.

Data from such studies were not included.

Given the above caveats it was felt appropriate and beneficial for discussion to take a broader overview of the results in the research reports cited.

Meta-analysis

Meta-analysis is a statistical approach to aggregate and analyse summary statistics from a number of studies [4]. It is especially useful where studies disagree with regard to the magnitude or direction of an effect. For instance, we have used the approach to compare glycaemic control with human and porcine insulins by means of data on glycosylated haemoglobin, fasting blood-glucose and mean blood-glucose levels in various reported studies [9] and to relate multiple injections with glycaemic control [8].

A meta-analysis is much more structured and replicable than an ordinary narrative literature review. Based on Chalmers and Lau [2] we have developed a ten step procedure for conducting meta-analyses:

- development of a protocol for conducting the meta-analysis;
- identification of sources of information used;
- definition of the criteria for the selection of trials for inclusion;
- reading, classification, coding, scoring, evaluating and choosing of literature;
- adjudication of differences among readers on the qualitative criteria;
- development of questions, procedures, and analyses to pose of trials for inclusion;
- reading of papers and answering of questions on the checklists;
- combination of results and quality assurance of the data;
- analysis, interpretation and reporting of results.

T2 DM

One of the difficulties in the development of general guidelines for the treatment of Type 2 diabetes (and the need for this research) is that, unlike T1DM, it develops gradually rather than suddenly; that is, we know when it is diagnosed but not necessarily when it commences. Thus, baseline data are ambiguous.
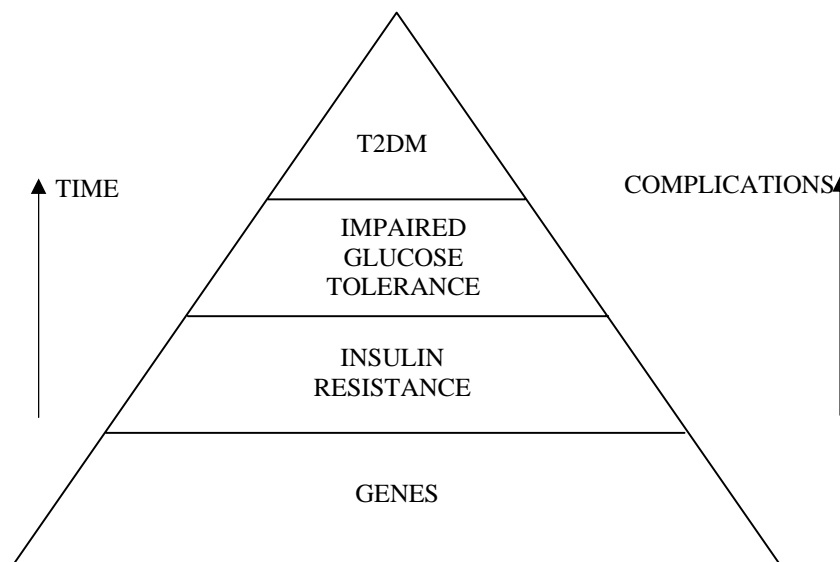

Fig. 1 The progress of T2DM

Fig. 1 schematically represents the progress of T2DM for those people who have the right 'cocktail' of genes to be predisposed to T2DM. (The nature versus nurture debate is as alive

here as it is in educational research. For instance, there is evidence, albeit circumstantial, that that the diet of the pregnant mother, particularly during the last six to eight weeks of pregnancy when the adipose and islet cells are formed, can also play a role in the subsequent development of T2DM in the offspring [10].

Some people who are genetically predisposed to T2DM become insulin resistant, fewer still develop impaired glucose tolerance (IGT), and then a few move on to get T2DM (or non-insulin dependent diabetes mellitus, NIDDM). If insulin resistant people adopt appropriate lifestyles of diet and exercise, then the onset of T2DM may be delayed and its complications, such as cardiovascular disease, avoided or, at least, minimised.

Methods
The data here have been combined by means of the following criteria:
- weighted averages (and ranges);
- data are not that accurate in the meta-analyses when combined so we have used integer values since decimal precision adds nothing to the picture;
- there are high rates of discontinuation in some studies;
- the effect of aspirin on the primary prevention of cardiovascular disease in people with diabetes was not included because some studies included both types of diabetes and others did not report the original diagnostic criteria..

By using weighted averages and ranges (weighted according to original sample size) we have a crude indicator of possible significant differences (but no measure of the extent of significance). Thus the counter-intuitive result for a slight increase in stroke events with the relatively greater intensive treatment in Table 1 is put into perspective when the ranges are considered.

Results
With this very conservative approach the "significant" differences are with those marked with '*' where the ranges do not overlap. The results are events per 1,000 person-years.

Table 1. Glycaemic Control (UGDP, VACSDM, UK PDS)

Type 2 DM (N=4,843)	Intensive Treatment	Standard (Placebo)
Coronary Heart Disease	17 (0,46)	18 (2,39)
Stroke	7 (0,29)	5 (0,11)
Total Mortality	19 (1,29)	20 (0,28)

Table 2. Blood Pressure Lowering (SHEP, Syst.Euro, HOPE)

N=9,364	Type 2 DM		Non-DM	
	Anti-hyperintensive	Placebo	Anti-hypertensive	Placebo
CHD	19 (4,18)*	26 (26,27)*	16 (10,21)	20 (11,27)
Stroke	10 (6,19)	16 (12,29)	7 (6,9)*	12 (9,15)*
Mortality	23 (21,35)	31 (28,45)	21 (19,22)*	23 (22,25)*

Table 3. Lipid Lowering Statins (4S, CARE, LIPID, VAHITS)

N=6,534	Type 2 DM		Non-DM	
	Treatment	Placebo	Treatment	Placebo
CHD	40 (31,55)	51 (38,71)	25 (20,35)	33 (23,49)
Stroke	12 (9,13)*	17 (15,23)*	5 (4,6)*	7 (6,8)*
Mortality	24 (24,24)	30 (30,30)	25 (14,31)	29 (19,35)

Table 4. Lipid Lowering Fibrates (VA-HIT, DAIS, SENDCAP HHS)

N=7,913	Type 2 DM		Non-DM	
	Treatment	Placebo	Treatment	Placebo
Combined end points	42 (7,55)	62 (21,76)	17 (5,35)	22 (8,45)

In so far as one can generalize in the absence of random sampling in the original studies, it can be observed that with these weighted averages:
- intensive glycaemic control does not have a major effect on cardiovascular disease;
- anti-hyperintensive agents have significant benefits in reduction of the primary end points;
- lipid lowering statins, but not fibrates, have significant effects in reducing strokes and marked effects in reducing coronary heart disease.

This is not to imply that there are no other benefits in these strategies but merely to confirm that their effects are not consistent in the limited number of relevant studies available. Furthermore, the above global approach obscures the subtleties which may be observed with particular agents in each category.

Comparison with Huang *et al*

Huang *et al* [5] also conducted meta-analyses. They searched MEDLINE (1966 to 2000) to identify randomized controlled trials in T2DM diabetes which compared intensive medication control of risk factor levels in standard therapy or placebo. Some of their studies were the same as those included in Briganti *et al* [1] and Colagiuri and Blest [3].

The results of our previous (above) approach accord well with those of Huang *et al* (except in two places) as can be seen in Table 5 in which the results are expressed as summary rate ratios.

Table 5. Comparison with Huang *et al*

%	Glycaemic Control		BP Lowering		Lipid Lowering (statins)	
	Huang	Above	Huang	Above	Huang	Above
CHD	0.91	0.94	0.76	0.73	0.60	0.78
Stroke	1.16	1.4	0.61	0.63	0.74	0.71
Mortality	0.94	0.95	0.51	0.74	0.80	0.80

Conclusion

From the source studies we can say that glycaemic control is clearly important in the reduction of risk for coronary heart disease and overall mortality as is blood pressure lowering for CHD and lipid lowering statins for overall mortality. A major problem is getting sufficient statistical power because of the small number of studies which have Level I quality of evidence.

The point of the foregoing analysis is to suggest that a global approach to the meta-analysis can be useful in its simplicity by highlighting the important points in the big picture. To delve further into those points is a separate issue for the diabetologist.

As an encouragement to statisticians to get involved in these rapidly developing areas of medical and social research, we conclude with the four point quality of evidence scale recommended by the National Health and Medical Research Council of Australia after adaptation from the United States Preventative Services Taskforce [6,7].

Table 6. Quality of Evidence rating Scale

Levels	Controlled Trials	Epidemiological Evidence
I	A systematic review of all relevant randomised trials	Systematic review of all relevant population-based studies
II	At least one properly-designed randomised controlled trial	A well-designed population based study or representative cohort study
IIIA	Well-designed, but not randomised, controlled trials	Well-designed case-control study, cohort study or less well-designed population based study
IIIB	Well-designed cohort or case-control analytic studies, preferably from more than one centre	
IIIC	Multiple time-series with or without intervention	
IV	Opinions of experts based on clinical experience or descriptive studies	Descriptive case series, clinical experiences, respected authorities

References

1. Briganti E., R. O'Brien, J. McNeil (2000). Options for a National Diabetes Vascular Prevention Strategy, Monash University, Melbourne.
2. Chalmers T., J. Lau (1993). Meta-analytic Stimulus for Changes in Clinical Trials, Statistical Methods in Medical Research, 2, 161-172.
3. Colagiuri S., J. Blest (2002). Lipid-lowering Therapy in People with Type 2 Diabetes, Current Opinion in Lipidology, 13, 617-623.
4. Glass G., B. McGaw, M. Smith (1981). Meta-analysis in Social Research, Sage, Beverley Hills.
5. Huang E., J. Meigs, D. Singer (2001). The Effect of Interventions to Prevent Cardiovascular Disease in Patients with Type 2 Diabetes Mellitus, The American Journal of Medicine, 111, 633–642.
6. Liddle J., M. Williamson, L. Irwig (1995). Evidence Evaluation Tool. Sydney, New South Wales Department of Health.

7. Mitchell P., J. Wang (1996). Clinical Practice Guidelines for the Management of Diabetic Retinopathy, Sydney, Department of Ophthalmology, University of Sydney.
8. Shannon A. (1986). Meta-analysis in Medicine, Journal of the Royal Society of Medicine, 79, 686.
9. Shannon A., S. Colagiuri, J. Miller (1990). Comparison of Glycaemic Control with Human and Porcine Insulins – a Meta-analysis, Medical Journal of Australia, 152, 49.
10. Shannon A., C. Wong, J. Wyndham (1997). Gestational Diabetes Mellitus: A Meta-analysis, New South Wales Department of Health, Sydney.

Abbreviations

BIP	Bezafibrate Infarction Prevention (study)
CARE	Cholesterol and Recurrent Events (study)
CHD	Coronary heart disease
CVD	Cardiovascular disease
DAIS	Diabetes Atherosclerosis Intervention Study
DM	Diabetes Mellitus
4S	Scandinavian Simvastatin Survival Study
HHS	Helsinki Heart Study
HOPE	Health Outcomes Prevention Evaluation Study
HPS	Heart Protection Study
LIPID	Long-term Intervention with Pravastatin in Ischaemic Disease (study)
SENDCAP	St Mary's, Ealing, Northwick Park Diabetes Cardiovascular Disease Prevention (study)
SHEP	Systolic Hypertension in the Elderly Trial
Syst. Euro	Systolic Hypertension in Europe Trial
UGDP	University Group Diabetes Program
UKPDS	United Kingdom Prospective Diabetes Study
VACSDM	Veterans Affair Co-operative Study
VA-HIT	Veterans Affairs High-Density Lipoprotein Intervention Trial
VAHITS	Veterans Affair HDL Intervention Trial
WOSCOPS	West of Scotland Coronary Prevention Study