Predicting the impact of polypill use in a metabolic syndrome population: an effectiveness and cost-effectiveness analysis

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Zomer: Polypill and metabolic syndrome

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Figure 1: Markov model of the effectiveness and cost-effectiveness of treatment with the polypill, and its components, versus no treatment in the prevention of cardiovascular outcomes in a metabolic syndrome population.

Abstract

Background: Individuals with metabolic syndrome (MetS) are at increased risk of cardiovascular disease (CVD), often requiring combination drug therapy for control of risk factors and subsequent risk reduction. This study aims to compare the long-term effectiveness and cost-effectiveness of the polypill (a multi-component tablet), and its components (alone or in combination), in a MetS population. **Methods and Results:** A Markov state transition model, using individual subject data from the Australian Diabetes, Obesity and Lifestyle study, was constructed to simulate the effects of the treatment versus no treatment on CVD events, and costs over 10 years. In 1991 individuals classified as MetS and free of existing diabetes or CVD, treatment with the polypill (or its components) was effective at reducing cardiovascular events (statin: 171, aspirin: 201, anti-hypertensive: 186 per 1000 individuals). The more drug therapies employed the greater the reduction with the polypill reducing up to 351 cardiovascular events per 10,000 individuals. Cost-effectiveness analyses were sensitive to drug treatment costs and effectiveness of treatment. At a cost of $AUD 42 per person per annum, aspirin was considered cost-saving. All other treatment strategies, including the polypill, were not cost-effective. **Conclusions:** The polypill is an effective prevention strategy for CVD at those of high-risk of disease. However, at a cost of $AUD 704 per person per annum, it is not considered cost-effective.

1 Introduction

The polypill, a multi-component tablet designed to reduce a number of cardiovascular risk factors simultaneously, was first described by Wald and Law in 2003. They demonstrated that a tablet containing a statin, three blood pressure lowering drugs, aspirin and folic acid could reduce a person's risk of coronary heart disease (CHD) and stroke by 88% and 80%, respectively[1].

The polypill has been accepted for use in the secondary prevention setting from inferences of safety of its components[2], but the balance between benefit versus harm remains uncertain in primary prevention. Large clinical trials in a primary preventive setting are currently ongoing, with a short (12 week) trial having been completed thus far. The Indian Polycap Study (TIPS)[3] was a randomised, double-blind clinical trial that assigned 2053 individuals aged 45 to 80 years without cardiovascular disease (CVD), but with at least one cardiovascular risk factor, to either the polypill (Polycap), or 8 other groups: aspirin alone, simvastatin alone, hydrochlorothiazide alone, different combinations of blood-pressure lowering drugs alone, or blood pressure-lowering drugs plus aspirin. Data from TIPS indicated that the effects of the polypill may not in fact be equal to the combined effects of its individual components as originally proposed by Wald and Law. That is, actual reductions in blood pressure and low density lipoprotein cholesterol (LDL-C) were lower than that projected by Wald and Law, resulting in a combined effects reduction in risk of CHD and stroke of 62% and 48%, respectively, in a primary prevention setting.

Metabolic syndrome (MetS), a cluster of risk factors for CVD and diabetes, is becoming increasingly prevalent as a result of rising rates of obesity and sedentary

lifestyles[4]. First-line management of MetS is aimed at lifestyle changes. If risk factors remain uncontrolled, treatment with therapeutic interventions that target individual risk factors are employed[5].

The aim of this study was to estimate the long-term (10-year) effects (both beneficial and harmful), and associated costs, of the polypill (and its components) from a healthcare perspective, in patients with MetS, compared to no drug treatment.

2 Methods

2.1 The model

A Markov state-transition model[6] (Figure 1) was constructed to simulate the impact of the polypill and its components on cardiovascular events and death over 10 years. All individuals entered the model in a 'healthy' state (with MetS but free of CVD) and could make transitions to the model's different health states during annual cycles. These included 'Alive without CVD, 'Alive with CVD', 'Dead from CVD' and 'Dead from other causes'. Decision analysis[7] was applied to compare the polypill against individual and dual-drug therapy versus no treatment. The individual and dual-drug therapy groups comprised aspirin alone, simvastatin alone, blood pressure-lowering therapy alone, aspirin plus simvastatin, aspirin plus blood pressure-lowering therapy, and simvastatin plus blood pressure-lowering therapy.

All individuals entered the model in the initial health state, 'Alive without CVD'. With each annual cycle, the probability of entering a different health state (mentioned above) was determined using risk prediction algorithms and population life-tables. All events were assumed to occur half-way through a cycle. Individuals continued to

cycle through the model until the time period of interest (10 years) was reached or when death occurred.

2.2 Modeled population

The model was populated with individual data from patients with MetS (microsimulation)[8] participating in the Australian Diabetes, Obesity and Lifestyle (AusDiab) study[9], a national, longitudinal, population-based study examining the natural history of diabetes and its complications, particularly cardiovascular complications.

Only subjects who were classified as having MetS (as defined by the Joint Interim Statement guidelines published in 2009; Table I)[10] and free of diabetes and/or CVD at baseline were included in the model. Individuals were excluded if they were currently receiving blood pressure-lowering or lipid-lowering therapy/ies.

The risk of cardiovascular events was calculated for each individual using the Framingham algorithms[11]. These estimate cardiovascular and mortality risk based on an individual's age, sex, smoking status, systolic blood pressure (SBP), total cholesterol, high density lipoprotein cholesterol (HDL-C), and the presence of diabetes and left ventricular hypertrophy (LVH). Subjects were simulated to develop myocardial infarction (MI), stroke, and fatal CVD using these algorithms. The onset of any of the events listed above also influenced the risk of subsequent events

In the first cycle, cardiovascular risk was calculated using baseline data from the AusDiab study. With subsequent cycles, each individual's age was increased by one

year. Modifiable risk factors (blood pressure and cholesterol) were also changed according to age-related trends derived from the AusDiab study[9]. That is, baseline data for SBP, total cholesterol, and HDL-C were stratified according to five year age-bands and annual changes within age-bands were calculated. All changes were assumed to be linear.

2.3 Risks of cardiovascular disease and death

Framingham algorithms[11] were used to calculate the risks of non-fatal CVD, comprising MI and stroke, and cardiovascular death. These algorithms have been shown to be the most appropriate cardiovascular risk prediction algorithms available for use in a MetS population[12]. Risks were calculated according to individual-specific data on age, sex, SBP, total cholesterol, HDL-C, smoking status, presence or absence of diabetes, and presence or absence of left-ventricular hypertrophy. With each annual cycle, cardiovascular risk was re-calculated according to age-related changes in systolic blood pressure, total cholesterol and HDL-C. These changes were determined according to AusDiab baseline data stratified by sex and five year age-bands. From these, annual changes within age-bands were derived. All changes were assumed to be linear.

The risks of dying from non-cardiovascular causes were calculated using national long-term, age- and sex-specific mortality data from Australia[13]. The most recent available data was from 2007. Due to lack of data stratified by history of cardiovascular disease, the assumption was made that they were the same for model subjects with and without cardiovascular disease.

The risk of secondary events such as recurrent non-fatal events and death (from cardiovascular and non-cardiovascular causes) among subjects with CVD was calculated using one year mortality data from the Reduction of Atherothrombosis for Continued Health (REACH) registry[14]. This was a prospective cohort study that followed individuals with at least three atherothrombotic risk factors and/or previous history of atherothrombotic disease for a period of two years, collecting morbidity and mortality-related data. As mortality data from the REACH registry were not specified for sub-groups, the assumption was made that all subjects with cardiovascular disease shared the same risks of death.

2.4 Intervention

Seven therapeutic strategies were compared (aspirin alone, simvastatin alone, a combination of three blood-pressure lowering drugs alone, blood pressure-lowering therapy plus aspirin, blood pressure-lowering therapy plus simvastatin, simvastatin plus aspirin, the polypill) to no treatment. Efficacy data associated with each strategy were derived from TIPS[3]. The relative risk reductions associated with combination therapies, including the polypill, were calculated using a simple multiplication of relative risk reduction estimates of the individual therapies. See Table II for detailed

input data. In the model, we assumed that all relative risk reductions applied to all subjects and were applicable as long as subjects were taking the therapy. It was also assumed the effects on CHD demonstrated in the TIPS study were the same for MI alone.

For therapies that included aspirin, either alone or in combination, age- and sex-specific risks of bleeding were calculated from the U.S. Preventive Services Task Force Recommendation Statement "Aspirin for the Prevention of Cardiovascular Disease"[15]. This was a review of the literature of clinical trials and the benefits and harms associated with aspirin use in the primary prevention. The evidence shows that aspirin use increases the risk for major bleeding events; primarily gastrointestinal bleeding in both men and women, and haemorrhagic strokes in men only. All risks increased with age.

2.5 Utilities

Utility weights for the various cardiovascular health states were derived from an analysis of quality of life data in a population with type 2 diabetes mellitus in the United Kingdom (UKPDS)[16]. Quality of life was assessed in this population using the EQ-5D multi-attribute utility instrument, a standardized instrument that uses simple descriptive profiles and preference weights to assign a single index value for health status between 0 and 1, where 1 implies the best state of health and 0 indicates the worst state of health. Negative states are those that are deemed worse than being dead. The utility associated with MI and stroke was 0.95 and 0.84 respectively, at the time of event and for each year thereafter. The utility associated with gastrointestinal bleeding was estimated from an analysis undertaken by Greving et al[17]. This

estimated the utility using time trade-off techniques[18,19]. Thus, as gastrointestinal bleeding results in only short-term morbidity, it was given a value of 0.94 for the year after the event to reflect 3 weeks deducted from overall survival.

2.6 Costs

The annual costs of single therapies were based on prices paid via the Australian Pharmaceutical Benefits Scheme[20]. Multiple therapies (more than one drug) were calculated by simply summing the costs of individual therapies. The precise annual cost of the polypill (a combination therapy) in Australia remains unknown. It has been suggested by Dr Reddy's Pharmaceutical Company, who will market the polypill, that the cost of the polypill will be less than the sum of the separate costs of the components in Australia (personal communication, Assoc Prof A Patel). With this in mind, we have modeled the polypill at a cost that is 25% less than the cost of the sum at present.

Costs of non-fatal events were gathered from a review on the direct costs of cardiovascular complications in a "healthy" population from a government perspective[21]. These were estimated for the year the event first occurred and subsequent years thereafter. The cost of a fatal cardiovascular event was taken from an economic analysis of chronic diseases in Australia[22]. All costs were inflated to 2012 values according to the health price index[23].

2.7 Cost-effectiveness analyses

The outcomes of interest were the incremental (net) cost per year of life saved (ICER: $/YoLS) and the incremental (net) cost per quality-adjusted life year ($/QALY).

QALYs recognize that a year lived with disease is not equal to a year lived in good health. Thus, where a year lived in good health is equal to 1, a year lived with disease is equal to 1 life year * utility ascribed to that disease state[24].

Future benefits and costs were discounted at an annual rate of 5%, as commonly recommended[25]. Discounting is undertaken in economic analyses to reflect society's preference for immediate, rather than delayed, benefits.

2.8 Sensitivity Analyses

@Risk 4.5 for Excel (Palisade, 2005) enabled probabilistic sensitivity analysis using 10% variation around relative risk reduction and cost inputs are outlined in Table 2. This is a conservative approximation of the true uncertainty surrounding these inputs. The effects of these uncertainty estimates were analysed by way of Monte Carlo simulation using 1000 iterations[26].

3 Results

Of the entire AusDiab study population at baseline, 3927 (35%) individuals were classified as having MetS. Of these, 767 had known or newly diagnosed (at baseline) diabetes, 737 had existing CVD and 1775 were on anti-hypertensive and/or lipid lowering therapy. With these individuals excluded, as well as those with any missing data for variables needed to predict cardiovascular risk or existing disease, the population of interest comprised 1991 individuals. Table III demonstrates that this was a relatively young and healthy population, with a mean age of 52 years and a low prevalence of smoking (18%). As all individuals met MetS diagnostic criteria, blood pressure, total cholesterol and HbA1c were expectedly high.

Compared with no drug treatment, all therapies decreased the number of cardiovascular events and deaths, and hence increased the number of years lived. The degree to which deaths were prevented was dependent on the risk reduction associated with therapy, as well as the risk prediction algorithm employed. For example, statin therapy alone could potentially prevent 151 (IQR: 115 to 176) non-fatal cardiovascular events and 20 (10 to 25) cardiovascular deaths per 10,000 individuals over 10 years, anti-hypertensive therapy (which included three drug therapies administered at half-dose) could prevent 166 (131 to 181) non-fatal cardiovascular events and 20 (15 to 30) cardiovascular deaths, aspirin therapy alone could prevent 176 (141 to 191) non-fatal cardiovascular events and 25 (15 to 30) cardiovascular deaths, and the combination of all of the above therapies (the polypill) could prevent up to 306 (226 to 392) non-fatal cardiovascular events and 45 (35 to 50) cardiovascular deaths per 10,000 individuals treated. All treatment therapies containing aspirin could also potentially cause 131 haemorrhages per 10,000 individuals treated.

Table IV summarises the results of the cost-effectiveness analyses. Aspirin, at a cost of $42.50 per annum was estimated to be cost saving. Statin alone had an ICER of $195,699/YoLS (IQR: 98,384 to 332,243) and $136,415/QALY (69,274 to 222,897), and anti-hypertensive therapy alone had an ICER of $342,791/YoLS (249,942 to 552,138) and $233,306/QALY (170,201 to 333,660). For combination therapy, an aspirin and statin (simvastatin) combination had an ICER of $112,386/YoLS (57,369 to 181,122) and $82,664/QALY (42,277 to 133,311), an aspirin and anti-hypertensive combination had an ICER of $215,937/YoLS (160,884 to 290,652) and $157,071/QALY (115,274 to 212,870), an anti-hypertensive and statin combination

had an ICER of $359,064/YoLS (275,707 to 475,857) and $253,520/QALY (195,981 to 330,563) and the polypill had an ICER of $304,978/YoLS (195,059 to 431,775) and $218,205/QALY (195,981 to 330,563).

Probabilistic sensitivity analysis demonstrates that even with variations in key inputs, such as the effect of the interventions on CHD and stroke, and costs associated with the intervention as well as disease, the results were robust.

4 Discussion

4.1 General discussion

This study describes the first long-term effectiveness and cost-effectiveness analyses of the polypill and its components in a MetS population, the importance of which is highlighted by the high burden of disease expected to arise from this population. The results indicate that in a MetS population, the most cost-effective therapy is aspirin, which could potentially be cost-saving, followed by statin (simvastatin) alone and anti-hypertensive therapy alone. Of the dual therapy combinations, aspirin plus statin would be most cost-effective followed by aspirin plus anti-hypertensive and statin plus anti-hypertensive. However, assuming that the cost of the polypill would be 25% less than the sum of its parts (equating to $704 per annum), it would be more cost-effective than the statin plus anti-hypertensive combination.

Nonetheless, all seven of the strategies tested in this study are unlikely to be cost-effective, based on the typical threshold maximum value of $50,000/YoLS[27]. This threshold may be conservative. According to the 'World Health Organization: choosing interventions that are cost-effective' (WHO-CHOICE)[28], interventions that

cost less than 3 times the gross domestic product (GDP) per capita are cost-effective. In the current Australian setting, this would mean that any intervention below $92,123 would be cost-effective.

A similar cost-effectiveness analysis found that a polypill costing $200 per person per annum would be cost-effective among those with >5% five-year cardiovascular risk or over the age of 55 years[29]. The MetS population is at a significantly higher cardiovascular risk, with an average five-year cardiovascular risk of 8.63%. However, the vast difference in the cost of the intervention therapy may explain why it is not cost-effective at an annual cost of $704.

In decisions regarding implementation of a health intervention, policy makers must determine whether the benefits for quality and longevity of life outweigh the cost of the intervention. This is important with respect to CVD, as there are high costs associated with non-fatal disease.

Another factor considered is any potential harm associated with the intervention. For example, the association between aspirin and increased risk of gastrointestinal bleeding has long been known[30,31]. The present analysis showed that although the risk of bleeding is increased with aspirin, either alone or in combination, these are generally outweighed by the benefits of preventing CVD.

4.2 Limitations

A major limitation to this research is that long-term effects of the polypill have only been hypothesized and to date, only short-term clinical trial results (12 weeks) are

available. However, evidence of the benefits of the polypill components are unequivocal. Less clear is the synergy of their effects.

The analysis was also limited by the lack of validated risk prediction equations specifically for a MetS population. The Framingham, although not intended specifically for use in MetS, was used to estimate cardiovascular and mortality risks as this represents a conservative estimate of the true risk in this high-risk population. This means that the risk calculated in this analysis using the Framingham equation may potentially be an under-estimation of the true risk in this population. The result would be an under-estimation of the cost-effectiveness (that is, an over-estimation of the ICERs) of the various interventions. Further to this, is the fact that the AusDiab population is a relatively 'healthy' cohort, with low observed incidences of cardiovascular events.

It is also important to note that indirect costs (such as productivity loss) were not included in the above analyses, thus contributing to a conservative estimate of cost-effectiveness.

Finally, there are always limitations with any type of modeling, which is based on conjecture. The present study addressed uncertainty by testing for reasonable variations to key data inputs via probablistic sensitivity analyses. This showed that the interventions being considered were unlikely to be cost-effective.

5 Conclusion

The polypill is likely to be effective in the reduction of cardiovascular events in a MetS population. It is, however, not cost effective. Nevertheless, in a high-risk population, among whom combination therapy is often prescribed, the polypill is likely to be more cost-effective than anti-hypertensive therapy alone or dual therapy with a statin and anti-hypertensive combination.

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The following is an outline of author contributions:

EZ developed epidemiological model and performed statistical analysis and drafted the manuscript.

AO participated in the design of the model and revised the manuscript.

DJM participated in data and subject selection and revised the manuscript.

CMR participated in the design of the model and revised the manuscript.

DL assisted in development of the epidemiological model and revised the manuscript.

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