Cost-effectiveness of interventions to prevent, screen and treat chronic diseases: A review

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Executive Summary

The current financial crisis across Europe and subsequent regimes of austerity pose a substantial and worrying threat to society's health by putting additional pressure on already overstretched health systems (1). Given the high prevalence of Chronic diseases such as cardiovascular disease and chronic obstructive pulmonary disease (COPD), ensuring interventions that tackle these diseases are both effective and cost-effective is key. However there is no consensus over how best to measure cost-effectiveness.

EConDA (Economics of Chronic Diseases) is a European Union co-funded project that aims to reach a consensus amongst experts over the best way to measure cost-effectiveness of interventions for chronic diseases.

This review, alongside a qualitative study of expert views, is the starting point for building this consensus. We have reviewed the cost-effectiveness literature related to interventions that aim to prevent, screen and treat at least one of four chronic diseases: type 2 diabetes (T2D), Coronary Heart Disease (CHD), Chronic Obstructive Pulmonary Disease (COPD) and Chronic Kidney Disease (CKD).

153 studies were reviewed in total; 29 for diabetes, 84 for CHD, 22 for COPD, and 18 for CKD. For type 2 diabetes, Intensive Lifestyle Management programmes and metformin tended to be cost-effective for prevention and management, while testing glucose or albulin levels was found to be a cost-effective screening method. For CHD, a wide range of interventions, such as low-cost statins and ACE inhibitors were cost-effective prevention strategies. Testing for C-reactive proteins was cost-effective as a screening method for CHD, while lipid lowering treatment was a cost-effective management intervention. For COPD, various methods of smoking cessation such as varenicline proved to be cost-effective for prevention, a walk-in spirometer clinic was cost-effective as a screening strategy and tiotropium was cost-effective for management of COPD exacerbations. For CKD, screening by testing glucose or albumin levels was cost-effective. As diabetes is a major risk factor for CKD, successful management of diabetes was also a cost-effective prevention strategy. Screening for CKD by testing glucose or albumin levels was cost-effective for selected groups, and irbesartan as well as satellite and nocturnal hemodialysis were cost-effective for management.

In general, cost-utility was the most widely used method, with 79% of studies reporting Quality Adjusted Life-Years (QALYs) as the outcome. 72% of studies took a healthcare approach and many studies were funded by the pharmaceutical industry, as opposed to a societal perspective. The time horizon of the study varied. The most common was a lifetime horizon, used by 57% of studies. 60% of the reviewed studies used a Markov model.

Limitations of these approaches were outlined which then formed the proposals for future work. It is suggested that a mixed-method approach with modelling, especially for prevention interventions where benefits occur over a life course, would be good practice. A societal perspective which incorporates costs beyond the health system will also be useful in gaining a broader picture of cost-effectiveness. Data limitations are however a major hindrance to carrying out robust cost-effectiveness analysis.

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Introduction

Non-communicable disease: challenges

The current financial crisis across Europe and subsequent regimes of austerity pose a substantial and worrying threat to society's health by putting additional pressure on already overstretched health systems (1). Therefore, ensuring that the way we intervene to prevent disease is both effective and cost-effective is increasingly important.

Of particular importance are chronic diseases – such as coronary heart disease (CHD) and respiratory disease – because they are the main drivers of morbidity and mortality across Europe – resulting in an estimated 86% of deaths and 77% of disease annually (2). Poor health behaviours such as tobacco use, overconsumption of unhealthy foodstuffs and alcohol are major causes of the chronic disease epidemic. Interventions that are effective in preventing chronic diseases and abating premature death are imperative if substantial health costs are to be avoided. Prevention will also increase revenue by expanding the healthy, productive work force. The cost of chronic diseases and their risk factors may have a significant impact on a country's GDP, and this has been estimated as between 0.02% and 6.77% (3).

Policy and decision makers need to make the best choice of where to allocate resources while still meeting the demands of the population. They need to review all possibilities and make rational choices that maximises utility. Multiple techniques to measure cost-effectiveness have been developed that help decision making. As part of the EU co-funded Economics of Chronic Diseases (EConDA project), work package 4, this review first outlines these various methods of measuring cost-effectiveness and then goes on to review the literature surrounding cost-effectiveness of interventions that prevent, screen and treat four important chronic diseases: coronary heart disease (CHD), chronic obstructive pulmonary disease (COPD), chronic kidney disease (CKD) and type 2 diabetes (T2D).

Methods

Key methods of economic evaluation

This review identifies several key characteristics included in each of the economic evaluations. These are the outcome measure, the discount rate, the perspective and time horizon used, and the modeling strategy. Each of these characteristics are briefly explained below[1].

Depending on how outcomes are measured, economic evaluations are categorized into three main groups: CEA (cost effective anaylsis), CUA (cost utility anaylsis), or CBA (cost benefit anaylsis). CEA use a clinical outcome, CUA use a measure of utility, while CBA use a monetary value. Table 1 gives an overview of each of these methods. Discounting is a practice that involves giving less weight to future costs and effects. Different countries often have their own guidelines for appropriate discount rates. The time horizon of a study refers to the amount of time after which the intervention is initiated that the costs and effects are measured. Different perspectives may be used in economic evaluations, mainly influencing the costs that are included in the analysis. For instance, the healthcare perspective only measures costs that are accrued in the healthcare system. Modelling of outcomes and effects is often required as the end-points of the clinical trial on which the evaluation is based are not sufficiently long.

In brief, according to the reviewed studies, the dominant discount rate for costs and effects, used by 55% of evaluations, was 3%. 63% of studies used a Markov modeling approach, 60% used a lifetime horizon, 85% used QALYs as their outcome measure (therefore employing a CUA), and 74% used the perspective of the healthcare system. There were also differences in the methods used between cost effectiveness studies of prevention, screening and treatment interventions. While it was still the most popular discount rate for each intervention type, many more screening interventions used the 3% discount rate (72%) compared with prevention (46%) and screening (47%) interventions. Screening interventions were also more likely to have used the healthcare perspective (84%) in comparison to prevention (72%) and management (65%). Markov modeling was used proportionally more in treatment interventions (74%) than in prevention (55%) or screening (60%). Finally, compared with screening (92%) and treatment (94%), economic evaluations of preventative interventions used the QALY less as an outcome measure (70%), instead favoring DALYs, LYG and other outcomes.

[1] Refer to the appendices for a more thorough explanation of each characteristic and of economic evaluations in general.

Search strategy

Pubmed, *Google Scholar* and article bibliographies were searched for articles that measured the cost-effectiveness of interventions that prevent, screen or treat the four chronic diseases of interest: type 2 diabetes (T2D), Chronic Obstructive Pulmonary Disease (COPD), Coronary heart disease (CHD) and Chronic Kidney Disease (CKD). Authors were contacted for further details and copies of papers where they were not open access.

Table 1 Overview of Economic Evaluation Methods

Economic Evaluation Method	Comparison	Measurement of Health Effects	Economic Summary Measure
CEA	Used to compare interventions that provide a common health effect	Health effects, measured in natural units	ICER; Cost per case averted; Costs per life year saved
CUA	Used to compare interventions that have morbidity and mortality outcomes	Health effects, measured as years of life, adjusted for quality of life	ICER; Cost per QALY; Cost per DALY
CBA	Used to compare different programmes with different units of outcomes (health and non-health)	Monetary	Net benefit or cost benefit-to- cost ratio; cost-saving

The following search terms were entered into Pubmed: cost-effectiveness methods, cost-effectiveness analysis, cost-benefit analysis, cost of illness, cost benefit analysis, modelling, methods of economic evaluation for prevention of chronic diseases, prevention, chronic disease methods of economic evaluation for prevention of chronic diseases, chronic disease prevention, economic evaluation, diabetes, coronary heart disease, chronic obstructive pulmonary disease, chronic kidney disease

Studies before the year 2000 were excluded unless related to a major study. A major study refers to a relevant, large and on-going study resulting in numerous publications; for example, the Diabetes

Prevention Program[2]. Studies had to assess costs and outcomes of prevention, screening, treatment strategies either short or long term. Only studies published in English were included. Studies of pregnant women were excluded.

153 studies were reviewed in total; 29 for diabetes, 84 for CHD, 22 for COPD, and 18 for CKD.

Disease outline and review results

Type 2 diabetes

Introduction

Type 2 diabetes (T2D) has been escalating rapidly in recent years. Current numbers of T2D patients are estimated to double and reach 350 million around the world by 2030. Surveys show that many people are unaware of their condition (5).

Lifestyle Modification Interventions (i.e. diet and/or physical activity) are effective in delaying or preventing the onset of diabetes and are effective in tackling prediabetes (6-8) and are at least as effective as pharmacological interventions (7).

Prevention of T2D

16 studies were reviewed and are presented in table A2 of the supplementary information, four of these were systematic reviews (D2, D3, D14, D17)(6;9-11).

[2]The Diabetes Prevention Programme (DPP, D1), crried out in the USA, is one of the major studies on T2D prevention. The objective was to determine whether weight loss through diet, physical activity or oral diabetes medicine, metformin, could prevent or postpone T2D among overweight participants with high blood glucose, i.e. prediabetes (4). All participants were overweight and had prediabetes. With a randomised control trial design (RCT) they were divided into three groups: 1. Aim to lose 7% of body weight and sustain loss by diet, physical activity and behavior change; 2. take 850mg metformin twice a day; 3 placebo pills instead of metformin. The latter two groups were also instructed on diet and physical activity, though without intensive motivation.

Outcome measure

All 16 studies reported costs and QALYS as outcomes, thus employing a cost-utility analysis.
Seven studies (including the 2 reviews) presented the results as the incremental cost-effectiveness ratio (ICER), i.e. the ratio of the differences in costs between two alternatives to the differences in effectiveness between the same two alternatives, usually presented as ICER per QALY gained (D11, D12, D13, D6, D14, D8, D3)(9;11-16). One study employed a CEA calculating ICERs based on cost of life years gained (LYG)(D5)(17).

Time Horizon

A range of different time horizons were tested, from 4 months (D13)(13), 1-5 years (D15, D10, D11)(16;18;19), 10-30 years (D20, D7, D6, D16)(15;20-22) or over a lifetime (D9)(23). The four systematic reviews (D2, D3, D14, D17)(6;9-11) included studies using time horizons ranging from less than a year to a lifetime.

Discounting

5 studies discounted at 3% for costs and effects (D12, D6, D5, D8, D9)(12;14;15;17;23), one study discounted only outcomes at 5%, one other did not discount at all. Two studies used different discount rates for costs and outcomes, and also for the different countries taken into consideration (D4, D5)(17;24). A range of discount rates were used in the systematic reviews, from 0-8% (D2, D3, D14, D17)(6;9-11).

Perspective

The perspective adopted was that of third party reimbursement[3] by two studies (D5, D11)(16;17), six studies adopted the national health care payer or system perspective including UK NHS, and healthcare system in US and the Netherlands (D3, D4, D6, D7, D13, D20)(11;13;15;22;24). One study each adopted a public payer perspective (D12)(12) and a partial societal perspective not including the opportunity cost of the patients' time(D5)(17). The remaining systematic reviews contained a range of perspectives (D2, D14, D17).

Modelling

[3] Such as an insurance company.

Eight studies used modelled estimates of cost-effectiveness (D22, D16, D11, D6, D7, D15, D12, D8, D9)(12;14-16;21;23;25;26), 3 of these used Treeage[4] (D11, D7, D15)(16;18;20) and 2 used Archimedes[5] (D22, D16)(21;25). The remaining studies used either used a Markov model (D5, D6, D9, D11, D12)(31;16;19;24;25) or a simulation model (D8)(18). The systematic reviews contained multiple model types, mostly Markov models (D2, D3, D14, D17)(6;8;9;11)

Cost-effectiveness

D14 (9) was a review measuring the cost-effectiveness of interventions to prevent and control diabetes (as recommended by the American Diabetes Association), and reviewed 56 studies from 20 countries between 1985 and 2008. D3 (11) was a systematic review of non-pharmacological interventions to reduce the risk of diabetes in individuals at high risk (with IGR). 9 RCTs were reviewed that compared LMI with standard care. D4 (24) reviewed 44 studies exploring the cost-effectiveness of individuals with different levels of diabetes risk between 2005and 2010. Each looked at cost-effectiveness in terms of CBA and CUA and in general concluded that prevention strategies (lifestyle intervention, metformin), either at the population level or in high risk individuals (IGR) were cost-effective. Saha and colleagues (D2) (6) identified 46 studies from a number of countries - USA, China, India, Japan, Sweden, Finland, the Netherlands and the UK - that measured the cost-effectiveness of lifestyle interventions to prevent T2D . They reported that diabetes prevention interventions that are either targeted or universal screening or community based interventions are cost-effective. However, the authors note the difficulty with comparing results of these studies because of the type of intervention, means of provision, target groups, setting and methodology.

Eight studies used the DPP methodology (D9, D11, D7, D15, D16, D10, D5)(16-21;23). Three studies evaluated a lifestyle intervention (diet and exercise), one in patients 60 years of age and older(D8)(14) and two in high-risk individuals (High IFG) (D6, D13)(13;15). Two studies focused on physical activity only interventions (D12, D17)(8;12). Herman and colleagues (27) reported that if all participants of the DPP study were treated with a placebo, 50% would develop T2D within seven years. Lifestyle interventions would delay the manifestation of T2D among 50% for 18 years and metformin would postpone onset of T2D by 10 years among 50% of patients.

[4] Treeage is a software tool that allows for analysis of decision trees and Markov models.
[5] The Archimedes model is an online tool that combines real world and simulation data to create evidence.

Palmer and colleagues (D11)(24) used probabilities from the DPP to simulate the 3 scenarios in order to test the cost-effectiveness of LMI and Metformin in European countries (the UK, Germany, France, Switzerland) and Australia. Diabetes-free life years and extended life expectancy increased, which was shown to be cost saving in all countries except the UK (28)(D5). Possibly this is because of the difference in discount rates between the UK and other countries in this study making cross-country comparison difficult.

All studies, except for two (D13, D16)(13;21) concluded that prevention in terms of metformin or LMI was cost-effective relative to standard care or a placebo, at least in individuals below 65 years (D9)(23), and that lifestyle interventions dominate over metformin over a lifetime. The study performed by Irvine *et al.* (D13) (13) was a UK study and so used the UK CE threshold which is relatively low. Furthermore the study sample was small and there were a number of uncertainties. Eddy and colleagues (D16)(21) concluded that the DPP was not cost-effective, which differs from the other CE studies of DPP (D9, D11, D7, D15, D10, D5) (16-20;23) reviewed here, reporting a much higher ICER per QALY than other studies (62,600 US$/QALY compared to 8,800 US$/QALY). This may be because they used a 30 year time horizon whereas others have used a lifetime (D5, D9)(17;23).

Screening of T2D

Early screening for prediabetes or T2D, which can involve a blood test identifying a fasting glucose level from 6.1 mmol/l (110 mg/dL) to 6.9 mmol/l (125 mg/dL)(29) can delay complications and the occurrence of the disease as well as other related conditions such as coronary heart disease or chronic kidney disease. Factors such as older age, overweight, hypertension, family history and ethnicity are all risk factors for T2D. Screening may be more cost-effective if directed to these groups (D23)(30). Eleven studies were extracted and are listed in table A4 of the appendices.

Outcomes Measure

All of the studies included QALYs as an outcome measure except for one which reported DALYs (D25)(31). Therefore all studies employed a cost-utility analysis. Two studies included other analysis also, such as CEA measuring life years gained (D31)(32) or ICERs (D30)(33). No study used a CBA.

Time Horizon

Two of the reviewed studies took a lifetime horizon (D30, D31)(32)((33) , while two others took a 50 year horizon (D24, D25)(31;34). One each took a 40 (D23)(30) and 30 year (D26)(35) horizon and five of the studies were not clear about the time horizon used (D27-D29; D32, D33).

Discounting

Most studies were consistent at 3 % discounting (D24, D25, D26, D28, D29, D30, D31)(31-38) though two discounted at 3.5% (D27, D23)(30;39) keeping in line with the UK NICE guidelines.

Perspective

The perspective of the health system was adopted by all studies that explicitly mentioned the perspective (D24, D25, D26, D29, D30, D31)(31-36;38). Of these, one study adopted NHS perspective (D23)(30) and one mentioned that the perspective adopted was of a single payer health care system.

Modelling

Seven studies used a simulation model approach: Markov (D24; D29; D30)(33;34;38), Archimedes (D26)(35), hybrid decision tree/Markov model (D27)(39) and Monte Carlo methods (D28; D31)(32;32;37). One study presented results as the probability of each strategy of being CE at a given threshold. All studies found screening to be cost-effective, with screening of prediabetes with LMI or metformin for certain age groups or particular risk factor to be most CE.

Cost-effectiveness

10 studies were reviewed that explored the cost-effectiveness of screening programmes for prediabetes (IFG) or T2D (D23, D24, D25, D26, D27, D28, D29, D30, D31, D33)(31-39). These studies are summarised in table A3 of the supplementary information. Studies were carried out in Canada (D24)(34), Australia (D25)(31), the USA (D26; D29; D31)(32;35;38), the UK (D30)(33), Taiwan (D28)(37)and in a hypothetical populations (D27)(39). Two literature reviews (D26, D23)(35;36) and one commentary (D32)(40) were also reviewed since they discussed the cost-effectiveness of type 2 diabetes screening.

A commentary concluded that screening for T2D is cost-effective due to evidence that prevention of diabetes in high risk individuals is undeniable especially if started between the ages of 30 to 45 years (D33)(41). However, there are different factors that determine impact upon cost-effectiveness: screening was shown to be more cost-effective at younger ages than at older age groups (D23; D24;

D26; D28; D31; D30)(32-37), and if screening is repeated every 3-5 years in non-IFG individuals (D24, D26)(34;35) or those with a risk factor such as hypertension or obesity (D23, D24)(34;36).

In their literature review of economic modelling of screening for T2D Waugh and colleagues D23(30) identified four studies up to the year 2005, three that assessed the long-term CE of screening and one which considered only the long-term outcomes of implementing screening policy at the population level (D28, D31, D30, D33)(32;33;37). They found that detecting IFG is cost-effective with an ICER of £2266 per QALY gained, not just because of prevention of T2D but also because it reduces the risk of cardiovascular disease (D23)(36).

Management of T2D

Management of T2D is an important factor in reducing the burden of the disease. Multiple studies have been conducted to evaluate strategies for the treatment of T2D.

Two articles were extracted which evaluated strategies for treatment of T2D, both of which were from The Netherlands (D34; D35)(42;43). These studies are presented in table A4 of the supplementary information.

Outcome Measure

Both of the cost-effectiveness studies employed a cost-utility analysis, presenting outcomes in terms of ICERs per QALYs gained.

Discounting

The costs and effects for both evaluations were discounted at 4% and 1.5% respectively, in line with the Dutch guidelines for economic evaluations.

Perspective

The perspective adopted by both studies was that of the Dutch health care system.

Time Horizon

Both studies used a lifetime horizon.

Modelling

One study used a Markov model (D34)(43) while the other used a Dutch-specific diabetes microsimulation model (D35)(42).

Cost-effectiveness

D34 (43) projected the health care costs associated with 7 different lifestyle interventions for T2D patients over the life-course. Although health care costs were projected to increase for all scenarios due to increased survival rates, a range of interventions remained cost-effective. These included a 6-week structured self-management education programme and a 2-year structured counselling intervention to promote physical activity, with the ICER for each calculated to be €10,000 per QALY. At a threshold of €20,000 per QALY, both had a 99% probability of being CE. The second study (D35)(42) tested a Diabetes Control Protocol intervention versus usual care over 1 year. This is a multifaceted computerised decision support diabetes management intervention which reduces cardiovascular risk of T2D patients. Authors performed a CUA of DCP and the intervention was found to be cost-effective (increased QALYs) over usual care.

Coronary Heart Disease

Introduction

Coronary heart disease (CHD) is the most common of cardiovascular diseases. One of the leading risk factor of CHD is hypertension and by 2025 it is estimated there will be 1.54-1.58 billion sufferers globally, a 60% increase from the estimates in 2005 (44).

Prevention of CHD

Prevention of CHD may be pharmacological (e.g. statins) and lifestyle modifying. Statins are recommended to be used in both primary and secondary prevention of CHD for people at high risk and after an episode.

Sixty-four studies were extracted relating to the cost-effectiveness of prevention of CHD. They are listed on table A5 of the supplementary information.

Cost-effectiveness

Twenty nine studies used cost-utility analysis, 9 studies used cost-effectiveness analysis, 2 studies used cost-consequence analysis, 5 studies used cost-benefit analysis, 16 studies used two or more different methods.

Time Horizon

Eighteen studies used the lifetime horizon (CH1, CH20, CH22, CH24, CH31, CH33, CH37, CH38, CH39, CH40, CH41, CH44, CH46, CH56, CH59, CH60, CH61, CH64)(45-65) and the others use between 1-50 years depending on the perspective adopted in the study. One study also modelled different case scenarios using 7, 5 and 3 years as time horizons (CH8)(66).

Discounting

35 studies discounted for the costs and outcomes, wherein they have been discounted at 6% for one study (CH2)(65), between 4- 5% for six studies (CH11, CH15, CH26, CH32, CH36, CH57)(48;56;67-71) and 3% for eighteen studies (CH8, CH10, CH13, CH16, CH20, CH21, CH24, CH29, CH31, CH37, CH52, CH54, CH55, CH56, CH58, CH59, CH60, CH61)(46;48;49;51;53;57;59;60;66;72-79). The National Institute of Clinical Excellence (NICE) recommended discount rate of 3.5% was applied in ten studies (CH1, CH4, CH5, CH9, CH 27, CH39, CH40, CH41, CH44, CH64)(45;54;58;62;63;65;80-83) all of which were conducted in UK. One study discounted only costs, all the rest discounted outcomes as well.

Perspective

Of the 61 studies reviewed 35 studies explicitly mentioned the perspective. Of these, 23 studies conducted the analyses from the perspective of the healthcare services in the country (CH1, CH2, CH3, CH4, CH5, CH10, CH11, CH12, CH13, CH15, CH18, CH25, CH26 CH27, CH31, CH33, CH37, CH39, CH49, CH50, CH57, CH61, CH64)(46;48;50;52;55;56;62;63;65;67;70;71;75;79;80;82-89). Only 6 studies adopted a societal perspective (CH29, CH36, CH43, CH46, CH59, CH60)(53;59;61;68;76;90) and one a partial societal perspective along with the health care services perspective of the country (CH39)(63). One study each adopted a managed care decision maker perspective (CH8)(66) and the perspective of the Ministry of health (CH55)(78). Three studies also adopted a public sector perspective (CH34, CH37, CH38)(45;85;91) and another adopted that of an agency wanting to implement a programme already

implemented by another (CH63)(92). Third party payer perspective was adopted by three studies (CH20, CH21, CH24)(51;57;60).

Modelling

There is a clear indication of use and type of a model in approximately 60% of studies included in this review. The remaining have either not made their modelling methods available or have not included a detailed description of the method used. The most popular methods used were Markov modelling including State transition Markov model, multi-state life-table-based Markov model or Markov type model developed specifically for CHD, the Coronary Heart Disease model and 'KIMCHI' or CRIVM chronic disease model (CH1, CH4, CH5, CH11, CH13, CH14, CH15, CH16, CH20, CH21, CH24, CH25, CH27, CH32, CH33, CH35, CH36, CH37, CH38, CH41, CH45, CH46, CH55, CH57, CH60, CH61)(14;46;47;51-54;56;57;60;61;65;67-70;75;77;78;80;82;83;85;93-95). Three studies used a risk model software by WHO (CH52, CH53, CH54)(72;73;96), two studies each used a decision tree analysis (CH12, CH39)(63;86). Willingness to pay was elicited using a questionnaire in one study, responses from which were analysed statistically in one study (CH51)(94), in life table model analysis in two studies(CH31,CH56)(48;49) and the remaining used unspecified decision analytic model or a generic model.

Cost-effectiveness

Sixteen studies on statins with full economic evaluations were considered for this review. Eight were based on results from various trials and on-going or recently concluded studies - STELLAR (CH10, CH12)(79;86), FINRISK and 4S study (CH11)(70), IDEAL (CH16)(74), HPS (CH18)(87), WOSCOPS, AFCAPS, LIPID, CARE, 4S (CH19)(97), ALLIANCE(CH8)(66) and WOSCOPS (CH5)(80). One study compared primary prevention strategies across different drug classes (CH2)(88), four studies modelled on primary prevention with statins (CH5, CH9, CH14, CH15)(56;80;81;95) and two on statins in secondary prevention - (CH3,CH16)(74;74;84;97), whilst two studies discussed both primary and secondary prevention (CH1,CH12)(65;86). Three studies assessed cost-effectiveness of 40 mg/day simvastatin vs. other high dose statins (CH4,CH11,CH16)(70;74;83) and placebo (CH17)(98). One study estimated the cost-effectiveness of atorvastatin with respect to other generic statins before the patent expiry of atorvastatin (CH8)(66), and one study assesses the same for atorvastatin after the patent expiry, but in comparison with the in-patent rosuvasatin (CH10)(79). Two studies conducted cost-effectiveness analysis for different types of statins (CH12, CH19)(86;97). Amongst the studies conducted on the cost impact of aspirin, three modelled the costs and outcomes of co-therapy with a Proton Pump Inhibitor (CH20, CH24)(51;60) or statins (CH21)(51;57;60). All studies found low cost statins to be cost-effective.

Some studies also found branded statins to be cost-effective in the long run or after patent expiration. One study found that an intervention that increases adherence to statins is not cost-effective.

Two studies (CH22, CH23)(64;99) specified aspirin modelling in a primary prevention set up. Both found administration of low-dose aspirin to high-risk patients to be dominant in terms of cost-effectiveness over standard care. One study modelled gender specific outcomes, finding more favorable ICERs for aspirin treatment for men at a given age than for women (CH25)(89). Three studies performed an economic evaluation of ACE inhibitors in secondary prevention (Ramipril: CH26(71) Perindopril: CH27(82), CH28(100)). One of these studies, based on the HOPE (Heart Outcomes Prevention Evaluation) trial, found that the calculated ICER for the addition of ramipril to the medication of high risk patients compared favorably with those of other widely used treatments (CH26)(71). The remaining two were based on the EUROPA trial (CH27, CH28)(82;100). They both found that while the use of ACE inhibitors increased costs for secondary prevention of CHD, the estimated ICERs were well below normal threshold levels and therefore perindopril is highly likely to be a cost-effective intervention.

One study which focused on primary prevention with fibrates for patients with low levels of HDL-cholesterol, found use of generic gemfibrozil therapy cost-effective at all ages and sex categories using a threshold value of US$50,000 (CH29)(76).

A further study, conducted in the Netherlands, analysed the cost-effectiveness of the use of polypills in primary prevention of CHD in patients with a 10 year risk of cardiovascular death of 5%, 7.5% and 10%. (CH30)(101). In all scenarios the ICER was found to be between €8,700 and €12,000 per QALY gained, with the most cost-effective outcomes seen for those patients with a 10 year risk of 10%.

Six studies based on the cost-effectiveness of dietary modification as a prevention strategy for CHD met the inclusion criteria (CH31, CH32, CH33, CH34, CH35, CH36)(48;52;68;69;91;93). One, based on the Lyon Diet heart study, looked at the cost-effectiveness of the Mediterranean diet compared to a western diet for those patients with a previous myocardial infarction (CH36)(68). The authors claim this intervention is highly cost-effective, with an ICER of €579 per QALY gained.

The evidence of cost-effectiveness of nutritional interventions is mixed. Twenty three interventions for promoting fruit and vegetable intake in adults were assessed in a literature review and modelling study (CH31)(48). The findings suggest that the majority of these interventions are not cost-effective, with

only five out of the twenty three interventions having and ICER below AU$50,000 per DALY averted. The economic evaluation of 10 Australian nutrition interventions was carried out in another study (CH32)(69) and 2 nutritional interventions in yet another (CH33)(52). These studies conclude that all the interventions are highly cost-effective, with ICERs well below the WHO recommended threshold of 1/3 times GDP/capita (in this case AU$11,427-33,786 per QALY gained). The remaining two studies based on dietary modification modelled the impact of three public policies (CH34)(91) and telephonic intervention for low socio-economic communities(CH35)(93) respectively. The first of these studies finds that information campaigns represent the best value for money with an ICER of €3,000 per life year gained, while the two alternatives policies of a 3.4% reduction in VAT and a fruit and vegetable stamp policy having considerably higher ICERs (€99,000 and €403,000 respectively). The second study finds that the ICER for a telephonic intervention based on physical activity and diet, when compared to existing care, is AU$29,375 per QALY gained with 100% probability of being cost-effective at a threshold of AU$64,000 (CH35)(93).

Only two studies on smoking cessation met the inclusion criteria (CH43, CH44)(58;90) and both studies evaluated patient based interventions implemented as an intervention for secondary prevention upon discharge from hospital after a first attack. These studies both arrived at relatively low ICERs, €280 per LYG and US$5,050 per QALY respectively. These ICER values compare favorably with those other CHD interventions such as hypertenstion medication (US$10,000-60,000 per QALY gained). One study (CH42) originally shortlisted for inclusion is a modelling study that estimated economic burden of passive smoking in the US and not the cost-effectiveness of interventions and therefore is not considered further.

A number of trials were conducted on salt reduction. Twelve studies were considered for this review (CH45, CH46, CH47, CH48, CH49, CH50, CH51, CH52, CH53, CH54, CH55, CH56)(49;50;55;61;72;73;78;94;96;102-104), all modelled the cost and benefits for population-level salt intervention in country specific populations. Except for one study that didn't incorporate potential savings (87), each found that a reduction in salt intake dominates standard care by saving costs in the health system as well as averting deaths.

Five studies on physical activity (CH37, CH38, CH39, CH40, CH41)(45;47;54;63;85), public or community based interventions were included. The evidence on the cost-effectiveness of these interventions varies by paper. Four of the studies find that the majority of the interventions have ICER values below the

relevant thresholds, and claim that they are therefore cost-effective (CH37, CH38, CH41, CH40)(45;47;63;85). The remaining study presents only weak evidence of the cost-effectiveness of physical activity promotion in primary care, with a 64.7% probability that a 5 year universal strategy would be cost-effective at a threshold of £30,000 per QALY (CH39)(74).

Eight weight loss studies on the cost-effectiveness of interventions directed at prevention of CHD are included in this review (CH57-CH64) (57-61), the majority finding evidence for cost-effectiveness. All were population level interventions, two were gender specific and only analysed overweight in women (CH58, CH59)(59;77). The first of these found that an intervention comprised of diet, exercise and behavior modification for women resulted in the most favorable ICER of US$12,600 per QALY gained (91). The other found that a 16 week weight-loss intervention programme had an ICER of $1,862 per LYG (92). A further study, based on an internet-based weight management intervention which is an area of interest in this age of the internet (CH63)(92), found an ICER of US$25.92 per kilogram of weight lost. One Australian study did not find evidence of the cost-effectiveness of two weight loss programs that incorporated dietary and exercise counseling, with both programs having ICERs of over AU$100,000 per DALY averted.

Screening of CHD

A total of 9 studies were selected to be included in this review and are presented in table A6 of the supplementary information.

Outcome Measure

Six studies employed QALYs as an outcome measure, using a CUA (CH68-CH73)(105-110). One study was a CEA using life years saved (CH66)(111). The remaining study did not make the outcome measure clear (CH67)(112).

Time Horizon

Three studies modelled on a lifetime horizon (CH68, CH70, CH72)(106;108;113), two studies used a 30 year horizon (CH69, CH73)(105;107) and two others used a 5 year horizon (CH66, CH67)(111;112). The remaining study did not state the time horizon (CH71)(109).

Discounting

Four studies discounted for the costs and outcomes both using a 3% rate (CH68, CH69, CH70, CH72)(106-108;113). The remaining studies do not give a clear indication of the discounts used.

Perspective

Four studies adopted a societal perspective (CH66, CH67, CH68, CH72)(106;111-113) and one study conducted the analyses from the perspective of the healthcare services in the country (CH69)(107;111).

Modelling

Five studies used one of the various types of Markov models including CHD model (CH68, CH69, CH70, CH72, CH73)(105-108;113). Two studies used a decision analytical model (CH66, CH67, CH71)(109;111;111;112).

Cost-effectiveness

Three studies assessed the economic aspects of C-reactive proteins as a CHD predictor (CH66, CH67, CH68)(111;112;114). Blake *et al*. found the most favourable ICER for 65 year old men at US$42,600 per QALY gained, with large ICER increases for other age and sex groups (CH68)(102). Ess *et al*. calculated considerably lower ICERs for this treatment aimed at men older than 45 years in Germany and Italy, €10,217 and €16,950 respectively (CH67)(112). Two studies conducted economic evaluations of Computed Tomography for identification of the clinical signs of CHD (CH70, CH71)(108;109). The first of these studies reached the conclusion that this intervention was not cost-effective, while the other only found evidence of cost-effectiveness for men, with an ICER of US$48,000. One study each analysed the cost implications of stress testing in intermediate risk patients (CH69)(107), measurement of Carotid intima-media thickness (CH73)(105) and blood pressure screening in adolescents (CH72)(113). Six studies used cost utility analysis and one was a systematic review. While stress testing proved to be cost-ineffective, both blood pressure screening and measurement of Carotid intima-media thickness were cost-effective at normal threshold levels.

Management of CHD

Eleven studies were included in this review and are presented in table A7 of the supplementary information.

Outcome Measure

Five studies used a cost-utility analysis (CH75, CH77, CH82, CH83, CH84)(115-119), five used cost-effectiveness analysis (CH76, CH78, CH79, CH80, CH81)(120-124) and one other used both (CH74)(125).

Time Horizon

Three of the studies modelled a lifetime horizon (CH79, CH82, CH83)(117;118;122). One study each used a 3 year and 50 year horizon: CH75,CH77(115;116). Two studies each used a 10 year horizon (CH76, CH78)(120;121) and a 5 year horizon (CH80, CH81)(123;124).

Discounting

A discount of 3% was applied in four studies (CH74, CH75, CH79, CH83)(115;125) and one study discounted at 3.5% (CH76)(120). One study each use a 6% (CH81)(124) and a 2.5% (CH82)(117) discount rate. A further study uses a 5% rate for costs and a 1.5% rate effects (CH78)(121). One study appears not to apply discounting (CH80)(123).

Perspective

Five studies conducted the analyses from the perspective of the healthcare services in the country (CH77)(116). One study each considered the perspective of Medicare (CH75)(115) and an unspecified payer (CH74)(125). Two studies used the societal perspective (CH80, CH81)(123;124).

Modelling

Four studies used one of the various types of Markov models (CH74, CH75, CH78, CH80)(115;121;123;125). One study used a decision analytical model (CH77)(116) and one study used a CHD mortality model named IMPACT.

Cost-effectiveness

Two studies analysed the cost implications of lipid lowering treatment and other treatments to reduce mortality caused by CHD (CH74, CH76)(120;125). The first compared high-dose to low dose statin therapy in CHD patients. In the base case, high-dose therapy increased QALYs and costs, and at a threshold of 100,000 per QALY had an 80% probability of being cost effective (111). The second of these studies analysed the cost-effectiveness of a range of CHD treatments in an Irish setting. Aspirin, beta-blockers, ACE inhibitors, spironolactone, warfarin and statins were all found to be cost-effective, with ICERs below €6,500/LYG.

One study each looked at cost-effectiveness of drug eluting stents (CH75)(115) and cardiovascular magnetic resonance (CMR) using data from the CE-MARC study (CH66)(113). The first of these found that compared to bare-metal stents, drug eluting stents were not cost-effective, with an ICER of over US$1,000,000 per QALY gained. The second found the most cost-effective use of CMR for patients with CHD is following a positive or inconclusive exercise treadmill test, which is then followed by coronary angiography if the CMR is inconclusive or positive. This strategy gave an ICER below the lower end of the UK threshold range (£20,000 per QALY).

Four of the included studies reviewed the cost-effectiveness of beta-blockers treatment for patients with CHD (CH78-81)(121-124). These studies took place in Ireland (CH78)(121), Sweden (CH79)(122), US (CH80)(123) and the UK (CH81)(124). Each study found that the use of beta-blockers as an addition to current treatments was cost-effective, with one finding that this strategy dominated usual care (CH80)(123).

Three studies performed economic evaluations focused on anti-platelet drugs (CH82, CH83, CH84)(117-119). These therapies were reviewed as add-on treatments for those with acute coronary syndrome, and in one case specifically for patients undergoing a percutaneous coronary intervention. Each of these studies indicated that anti-platelet therapy was cost-effective.

Some therapies do not appear in the cost-effectiveness literature as interventions because they are now accepted into usual care, and are the standard by which other interventions are judged by.

Chronic Obstructive Pulmonary Disease (COPD)

Introduction

Around 75% of COPD is attributed to cigarette smoking (126). Old age is also associated with COPD. Symptoms are often considered states accompanying both smoking and ageing. For example, a persistent cough and breathlessness. Half of individuals displaying COPD symptoms are undiagnosed (127). COPD is often accompanied by other diseases especially since patients with COPD tend to be older.

Since smoking is a main cause of COPD, smoking cessation is effective in COPD prevention as well as premature death prevention (128).

Prevention of COPD

Smoking cessation programmes are key in COPD prevention and the impact of numerous smoking cessation strategies have been evaluated in this context. Seven articles were reviewed, from Australia (CO1) (129), the UK (CO2) (130), The Netherlands (CO3)(131), Germany (CO4)(132) and Sweden, Belgium, France, UK (CO5)(133), US (CO6)(134) and central America (CO7)(135) (Table A8 of the supplementary information).

Outcome Measure

All studies presented outcomes in terms of QALYs therefore employing a cost-utility analysis.

All studies used a lifetime time horizon, except for one which did not explicitly state the horizon used (CO7)(136).

Discounting

All studies discounted costs and effects equally. Two studies discounted at 3% (CO1, CO6)(129;137), two at 3.5% (CO2, CO5)(130;133), one at 1.5% (CO3)(138), one at 4% (CO4)(132) and another at 5% (CO7)(136).

Modelling

All studies used a Markov simulation. The Benefits of Smoking Cessation on Outcomes (BENESCO) model was used in a number of these studies. This model was developed to simulate the lifetime direct costs and consequences of a hypothetical cohort of US adult smokers who make a one-time attempt to quit smoking. The interventions modelled are varenicline, bupropion, NRT and usual care (136-138).

Perspective

One study adopted the perspective of the Australian health care system (CO1)(139), one adopted that of the US healthcare system (CO6)(134), and another that of the Dutch healthcare system(CO3)(138). Two other studies looked at multiple countries, and adopted the perspective of the health-care system of those individual countries under consideration (CO5,CO7)(133;136). One study adopted a societal perspective (CO4)(132).

Cost-effectiveness

Four studies explored the impact of different drugs in aiding smoking cessation (CO5, CO3, CO6, CO7)(131;133;134;136). All reported varenicline to be the most cost-effective over standard care, bupropion and NRT.

All of these studies found evidence of the cost-effectiveness of smoking cessation interventions, such as mass media campaigns (117) or with use of medication such as Varenicline (CO3, CO4, CO5, CO6, CO7)(132;133;136-138). In general, these interventions dominated standard care by reduce costs in health-care systems.

Two studies modelled the effectiveness of a range of smoking cessation services (CO2,CO4)(130;132). All interventions except for the combination of advice from a GP, self-help material and nicotine replacement therapy were dominant over the standard practice of doing nothing, with increased QALYs and reduced costs. More intensive counselling and bupropion resulted in larger dominance. Even the combination of advice from a GP, self-help material and nicotine replacement therapy was calculated to have an ICER of only £1,080, well below normal threshold levels.

One study from Australia modelled the cost-effectiveness of a mass-media anti-smoking campaign (CO1)(139) which was found to be both cost-saving and cost-effective.

Screening COPD

Screening and diagnosis for COPD requires measuring lung function with a spirometer which are widely available, but often not used (140) and COPD is significantly under-diagnosed (141). One study concluded that screening every patient at a surgery who reports being a smoker, on average one a day, would identify one patient a week.

Two studies were reviewed that measured the cost-effectiveness of screening smokers for COPD. One study was carried out in Sweden (CO8)(142) and one in Denmark (CO9)(143)(Table A9). Only the abstract was available in English for CO9(143), so the accessible information is limited.

Study Characteristics

The perspective for the article for which an English version was available was that of the health care provider (C08)(142). A CEA was utilized with effects reported as COPD cases detected. The model used was not specified in the article, and furthermore it was not clear if any discounting was performed or the time horizon used.

Cost-effectiveness

Study CO8(142) tested the effectiveness of a mini-spirometer in predicting the diagnosis of COPD in primary care patients at risk of COPD (smokers for ≥15 years). The reported ICER was £300 per COPD case detected. The study concludes that screening predicted COPD diagnoses and was cost-effective relative to standard spirometry measurement. A walk-in spirometry clinic was evaluated and was reported to be highly cost-effective (CO9)(143).

Management of COPD

More focus on management of exacerbations of COPD was found in the literature relative to studies of prevention and screening. Treatments of COPD vary depending on severity of the COPD. Smoking cessation programmes and pharmacological interventions such as roflumilast are aimed at reducing exacerbations.

Thirteen studies were reviewed and are listed in table A10 of the appendices.

Outcome Measure

Twelve studies carried out a cost-utility analysis presenting outcomes by QALYs (CO10, CO18, CO11, CO17, CO20, CO12, CO13, CO16, CO21, CO19, CO22)(144-151). Only the abstract was available for CO14 (152) so outcome measures are unclear.

Time Horizon

A range of time horizons were used in these studies. Two used a lifetime horizon (CO12, CO13)(146;149) and a 10 year horizon (CO10, CO21)(151;153). Four used a 1 year horizon (CO14, CO15, CO16, CO20)(150;152;154;155). One study each used a 2 year (CO17)(156), 5 year (CO18)(148) and 30 year (CO11)(147) horizon. The remaining studies were systematic reviews including a range of horizons (CO19)(157) and a 25 year horizon (CO22)(145).

Discounting

Two studies discounted at 3.5% (CO11, CO12)(146;147) and one study each at 3% (CO13)(149) and 1.5% (CO10)(151). One study used different discounts for costs and outcomes (4% and 1.5% respectively) (CO22)(145). Three studies did not discount (CO14-16)(150;152;154) and the remaining did not mention the discounts.

Perspective

The relevant health system perspective was adopted in the majority of the studies. The perspective was of the UK NHS in three studies (CO11, CO13, CO 20)(147;149) and of the German Social health insurance in one study (CO18)(148), Spanish NHS in one study (CO13)(149) and two studies (CO14, CO22)(145;152) employed general health system perspective. Societal perspective was taken by two studies (CO12, CO15)(146;154) with one employing both societal and third party perspective (CO17)(156) and a pure third party perspective was employed by one study (CO16)(150). Of the two systematic reviews, one used the health care perspective (CO22)(145), and the other used both the healthcare and societal perspective (CO19)(157).

Modelling

Seven studies used modelling techniques to simulate the cost-effectiveness outputs: one used a Markov-style stochastic dynamic population model (CO10)(151) five used a Markov model (CO11, CO13, CO16, CO12, CO18)(146-150) and one used Monte Carlo simulations (CO20)(155). The two systematic reviews used Markov modelling (CO19, CO22)(145).

Cost-effectiveness

Two studies were systematic reviews (CO19, CO22)(144;145) and are presented in table T10 of the supplementary information. The former reviewed 40 economic evaluations of drug therapy for COPD sufferers. Findings showed that tiotropium was related to reduced healthcare costs in most studies relative to other pharmacological interventions and a placebo. It was concluded that to compare results of differing interventions study methodologies need to be more consistent. The latter reviewed the long-term cost-effectiveness of 9 studies of smoking cessation services. CUA was employed and QALYs reported. Pharmocotherapy was most CE, followed by intensive counseling, then minimal counseling relative to usual care.

The interventions tested were either self-management lifestyle interventions including smoking cessation (CO17)(156) or smoking cessation only - testing the CE of varenicline (CO10, CO14, CO13, CO12, CO15, CO22)(145;146;149;151;152;154). Three studies test the CE of pharmacological interventions such as Roflumilast for individuals with moderate to severe COPD (CO11, CO16, CO18)(147;150;150). One study measured the CE of new technologies for COPD from 2001 to 2010 estimating the maximum price of a technology providing cure could achieve under the current CE rules. Interventions were reported to be cost-effective relative to placebo or other intervention.

Chronic Kidney Disease (CKD)

Introduction

CKD is an asymptomatic chronic condition gradually resulting in kidney failure with a worldwide prevalence of 8-16% (158). CKD is caused by reduced glomerular filtration rate (GFR) – so Type 2 diabetes and/or increased urinary albumin excretion (158) . It is detected either by a urine test for albuminuria or proteinuria or by a blood test for serum creatinine or estimated glomerular filtration rate (159-163). The most common cause of CKD is diabetes therefore the review above presenting literature on the prevention of T2D holds true in the following section on CKD as well. Screening can prevent disease progression and avoid kidney failure (164) while ACE inhibitors or Angiotensin II-receptor blocker (ARB) can slow down the progression of CKD.

Prevention

Primary prevention can involve controlling for diabetes and hypertension which are both main risk factors for CKD development. One study was reviewed that assessed the prevention of CKD (CK1)(165) which is detailed in table A11 of the supplementary information.

Study Characteristics

Using cost-effectiveness analysis the authors presented QALYs and ICER/QALY. The study used a lifetime horizon. The study adopted a health system perspective and discounted costs at 4% and outcomes at 1.5%. This study used a lifetime Markov decision model simulating the progression of CKD to test the most CE time to start an ACE inhibitor or ARB in patients with newly diagnosed T2D.

Cost-effectiveness

Three scenarios were assessed: treating all patients at the time of T2D onset; screening for microalbuminuria; screening for macroalbuminuria. The authors report that the most cost-effective method was to treat all as this had the lowest cost and highest benefits with a 70% probability of savings, dominating the screening scenarios.

Screening of CKD

Nine studies were reviewed related to the screening of CKD. These are presented in table A12 of the supplementary information.

Outcome Measure

Eight of the reviewed studies were CUAs presenting outcomes in QALYs (CK2, CK4, CK5, CK6, CK7, CK8, CK10, CK11)(38;166-171) and the remaining one being a CEA using LYG to measure effects (CK3)(172).

Time Horizon

The majority of the reviewed studies took a lifetime horizon (CK2, CK4, CK5, CK8, CK11)(168-171;173). The remaining studies take an 8 year (CK3)(172), 18 year (CK7)(167) and 60 year (CK10)(174) horizon.

Discounting

Discounting was carried out at 3% for five studies (CK2, CK5, CK7, CK8, CK10)(38;166-168;170) and two discounted at 5% (CK4, CK11)(169;171). The remaining studies did not mention the discount rate.

Perspective

Six studies adopted the perspective of the health system (CK2, CK5, CK8)(166;168;170) including one specifying Swiss Health Services(CK5)(170) whereas one study adopted the perspective of a Central Health Care Funder (CK4)(169). Another adopted a societal perspective (CK6)(175) and a final study adopted the perspective of a third party payer in the US (CK7)(167).

Modelling

Six of the studies used Markov based models, while the remaining three use the CKD Health Policy Model, a microsimulation model based on data from a US population.

Cost-effectiveness

There was variation across studies in whether screening was cost-effective for a whole population or just in at-risk group and this was dependent upon the type of test carried out. The cost effectiveness of screening for proteinuria is also dependent on the age of the target group. Most studies reported the screening to be cost-effective only in groups over 50 years of age (CK2, CK4, CK5)(166;169;170). In the USA, screening for proteinuria is estimated to be cost-effective in high risk patients or when screened at 10 year intervals or among people aged 60 and older. Hoerger and colleagues (CK10)(174) also recommended microalbuminuria screening and concluded its cost-effectiveness among diabetic and hypertensive patients. For this screening to be cost-effective for the rest of the population, it has to be carried out with time intervals (CK2)(173;176). In Switzerland it has been recommended to screen for microalbuminuria at age 50; twice a year for diabetic patients, once a year for patients with hypertension and with a 10 year interval for the rest of the population (170). Palmer *et al.* analyse the cost-effectiveness of urine dipstick screening for nephropathy targeted at patients with T2D and hypertension, followed by optimized treatment (CK20)(177). They find an ICER of US$20,011 per QALY gained for the intervention, and a 77% probability of cost-effectiveness at a threshold of US$50,000. A population based dipstick screening program for adults in Japan was found to cost-effective at the WHO recommended threshold with an ICER of US$12,660 per QALY gained (CK6)(175).

NICE concluded that in the UK screening non high-risk patients is not cost-effective (170) and screening should be limited to high risk patients (e.g. patients with diseases of renal tract, family history of CKD, T2D and T1D) to avoid negative effects of urine testing (178). In addition to these, the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (KDOQI) has recommended screening of subjects aged 60 and above. However, NICE does not consider age as a risk factor, just as it does not consider BMI, ethnicity or gender as risk factors (179).

Although initial screening tests such as eGFR or screening for albuminuria is not expensive, follow up induces high costs. Further testing such as biopsy and possible complications impose high economic burden. One should not overlook non-financial costs, such as cost of inconvenience or anxiety caused by the process and this should be included in cost-effectiveness analysis (166).

Applying guidelines from developed countries might not work for the rest of the world; other risk factors might be more important for a particular country or population.

Management of CKD

One of the main goals of CKD management is to avoid complications and reduce risk of CVD and kidney failure (169). End-stage renal disease can be avoided by early detection and treatment 69 (180). Glycaemic and blood pressure control can reduce risk of CVD mortality among patients with CKD. Lifestyle interventions such as controlling levels of salt and protein consumption are beneficial in management of CKD (164;181).

Eight studies were reviewed and are presented in table A13 of the supplementary information (CK12, CK13, CK15, CK16, CK17, CK18, CK19, CK24)(180;182-188).

Outcome Measure

Six of the reviewed papers used a CUA, with outcomes expressed in QALYs (CK12, CK16, CK17, CK19, CK20, CK24)(177;180;182;185;187;188). One of the papers was a CEA using LYG (CK18)(186). Two of the papers were systematic reviews, using a range of outcome measures (CK13, CK15)(184;189).

Time Horizon

Two of the papers used a lifetime horizon (CK16, CK24)(180;188). One uses a range of horizons from 5 to 10 years (CK17)(185). One papers each uses a horizon of 10 years (CK19)(187) and 25 years (CK20)(177). The two systematic reviews use a range of horizons (CK13, CK15)(183;184).

Perspective

The perspective used varies by study. One paper takes a societal perspective, considering productivity costs (CK12)(182). Two take the perspective of a third party payer (CK15,CK16)(180;184). Two papers takes the perspective of the UK NHS (CK13,CK24)(183;188), while another takes that of the Austrian public health system (CK19)(187). One study takes the perspective of a hospital (CK18)(186). The perspective is not made clear in the final paper (CK17)(185).

Modelling

All studies used a Markov model in their analyses, except for one study for which the modeling strategy was not clear (CK12)(182).

Discounting

A discount rate of 3% for both costs and effects was used in two studies (CK16, CK19)(180;187), and rate of 3.5% in two others (CK13, CK24)(183;188). One study uses a discount rate of 5% for both costs and effects, while another discounts costs at 6% and effects at 1.5% (CK17)(185). Two papers use a range of discount rates in the base case analysis. One uses 1.5-6% for effects and 3-6% for costs (CK15)(184). Another uses 6% for costs and 0.10% for effects (CK18)(186).

Cost-effectiveness

The first of these studies calculated the cost-effectiveness of an intervention in which CKD patients were closely tracked by a nephrologist and nurse-based multifaceted program focusing on applying evidence-based treatments (CK12)(182). Due a reduction in costs through fewer days spent in hospital, and no fall in the quality of life of the patients, the intervention was deemed to be dominant over standard care.

Of the reviewed articles, two were systematic reviews (CK13, CK15)(183;184). The first looked at the cost-effectiveness of a range of early referral strategies for patients with CKD. All potential referral practices were found to have an ICER of below £6,000 per QALY gained, with the lowest ICER of £3,806 per QALY occurring when every patient with an eGFR (estimated Glomerular Filtration Rate) lower than 30 ml/min/1.73m^2 was referred to specialist nephrology care unit (CK13)(183). The other systematic review studied the cost-effectiveness of the use of ibersartan, an angiotensin receptor blocker, to treat overt nephropathy in patients with T2D and hypertension in seven European countries and the US. As well as improving life expectancy in each setting, the intervention was found be cost-saving due to the reduction in end stage renal disease and was therefore dominant over usual treatment (CK15)(166).

Renal replacement therapy (RTT) is often vital for patients with CKD, especially those with end-stage renal disease. Four studies analysed the cost-effectiveness of a range of RTT options. Three of these studies focused on hemodialysis (HD)(CK16, CK17, CK18)(185;186;190). The first of these studies compared the use of home nocturnal HD (HMHD) to in-center HD in Canada using a long term perspective. Previous studies had looked at the cost-effectiveness of HNHD only in the short run. The study found that HNHD was both cost-saving and increased quality of life in the long-run (CK16)(180). The second study compared the cost-effectiveness of two renal replacement (RTT) therapies: HD and continuous ambulatory peritoneal dialysis (CAPD). As HD dominated CAPD in many of the simulations performed, increasing life years and reducing costs, the study concludes that this may be a more cost-effective treatment. The third study reviewed the cost effectiveness of hospital HD versus satellite HD

and home HD. Both home and satellite HD dominated hospital HD. When compared to satellite HD, home HD was calculated to have an ICER of £6,665 per QALY gained. The authors conclude that the results support a shift from hospital HD to these alternative therapies (CK18)(186). A further study reviewed the cost-effectiveness of a mix of RTT in Austria (CK19)(187). The standard practice in Austria comprises of approximately 90% of patients being treated with HD, 7% with peritoneal dialysis and 0.1% with a kidney transplant from a live donor. However, the treatment mix of 20% of new patients assigned to peritoneal dialysis, 10% with a transplant and the remaining being treated with HD was found to be cost-effective by saving costs and increasing QALYs compared to standard care.

A UK study looked at the cost-effectiveness of Lanthum Carbonate (CK24)(188), a noncalcium-based phosphate binding agent (LC), for second-line treatment of hyperphosphatemia after use of a calcium-based phosphate binder (CB). Hyperphosphatemia is a common condition for patients with CKD, involving electrolyte disturbance which increase both morbidity and mortality. The condition is usually treated with calcium-based phosphate binders. However, when these are ineffective dose escalation may occur which increases the risk of hypercalcemia. Therefore the use of a noncalcium-based phosphate binder is considered. Different QALYs were calculated for predialysis patients and patients on dialysis. For predialysis patients LC was found to be dominant compared to CB use in second-line treatment, mostly by delaying or preventing end-stage renal disease. For those patients already on dialysis an ICER of £6,900 per QALY gained was calculated for LC use.

Discussion

This review explored the cost-effectiveness of interventions to prevent, screen and treat CHD, T2D, COPD and CKD. The vast majority of the 153 studies reviewed concluded that the intervention in question was cost-effective. Only twelve studies reviewed interventions that were not cost effective. These were D13, D16, CK7, CK11, CH71, CH69, CH61, CH39, CH52, CH38, CH31, CH9 (13;21;47;48;54;72;81;107;109;167;167;171). However, we are mindful of the effects of publication bias, where interventions with null results are not published.

For type 2 diabetes, Intensive Lifestyle Management programmes and metformin tended to be cost-effective for prevention and management, while testing glucose or albulin levels was found to be a cost-effective screening method. For CHD, a wide range of interventions, such as low-cost statins and ACE inhibitors were cost-effective prevention strategies. Testing for C-reactive proteins was cost-effective as

a screening method for CHD, while lipid lowering treatment was a cost-effective management intervention. For COPD various methods of smoking cessation such as varenicline proved to be cost-effective for prevention, a walk-in spirometer clinic was cost-effective as a screening strategy and tiotropium was cost-effective for management of COPD exacerbations. For CKD, screening by testing glucose or albumin levels was cost-effective. As diabetes is a major risk factor for CKD, successful management of diabetes was a cost-effective prevention strategy. Screening for CKD by testing glucose or albumin levels was cost-effective for selected groups, and irbesartan as well as satellite and nocturnal hemodialysis were cost-effective for management.

79% of studies use a cost-utility analysis, reporting QALYs as outcomes. This is a useful tool since it enables comparison across disease areas. However the standard QALY has a number of limitations. It fails to capture equity concerns. For example, it takes no account of the initial health of a patient – a QALY is a QALY for everyone. It may be preferable from a societal perspective to give preference to the severely ill over others. The QALY also does not measure the process utility of interventions. For instance, the disutility of a particularly painful treatment is not captured in the QALY. Furthermore a QALY only measures the health produced by healthcare. Patients of long-term care may experience a large increase in wellbeing that is not measured by the QALY as their objective health has not increased. The QALY suffers from these drawbacks as it judges all interventions in a standardised way using a single summary measure. Taking a cost-consequence approach can allow for a wider consideration of effects. This suggests that a mixed-method approach is necessary and is something that emerged from the qualitative analysis (e.g. '*I've always been a proponent of a mixed-methods approach'* ID8).

72% of studies took a healthcare costs perspective, neglecting the impact of chronic diseases on the wider society, such as indirect costs. This possibly underestimates the cost-effectiveness of prevention strategies. Carrying out a cost-benefit analysis enables a societal perspective to be taken, and one expert from the qualitative analysis stated that '*taking a societal perspective is the gold standard*' (ID2)).

Although 13% of studies reported taking a societal perspective, often indirect costs were not mentioned explicitly and only aggregated costs were reported. This may be due to misuse of terminology, non-adherence to guidelines or difficulty in obtaining costs for items that cannot traditionally be measured in monetary terms. Therefore, due to lack of valid and reliable data availability, CBA might be inaccurate. Taking a friction cost approach was noted by three experts as a useful way to measure indirect costs.

In all the methods, the striking theme is the misreporting of cost inputs. For example, studies that claimed they employed a societal or public perspective often did not incorporate patient related costs, such as the time costs borne by patients and their relatives. This is likely due to poor quality data, lack of standardised collection procedures and well established and well defined terminologies.

Discount rates varied by study, with the most frequent discount rate being 3% for costs and effects, used in 51% of studies. The discount rate used is often based on the economic evaluation guidelines for each country. For example, in the UK the NICE guidelines specify that the costs and outcomes are discounted at 3.5% and utility values elicited for conducting CUA (191), while The Dutch guidelines specify that costs should discounted at 4% and effects at 1.5%. However, the discount rate by country was not uniform. For instance, the rates adopted in UK studies varied. Some also adopted the utility values from published sources which were not explicitly discussed. Since experts feel they need to adopt alternatives to what is prescribed, this suggests that there are limitations to the NICE approach requiring a re-evaluation and update of these guidelines.

The impact of chronic diseases stretches far beyond the health sector into sectors such as employability. Apart from direct medical costs, opportunity costs arise due to the patient being out of workforce, resulting in lower income for the patient and lost productivity in the economy. Some health evaluators have tried to capture this in their methods though the UK standardised guidelines of using CUA do not provide the flexibility to do so, this might be of consideration when assessing guidelines for chronic diseases.

The time horizon of studies is an important component for analysis especially in the case of public health interventions as the outcomes cannot be seen immediately after the intervention is implemented, and may in fact take years to accrue. Some evaluators have used different discounts for costs and effects, “differential discounting” and it is suggested that an immediate loss is weighed more heavily than a future gain (192), this deserves consideration here given that the benefits of chronic diseases accrue over a lifetime. There is a scarcity of long term studies conducted in the sphere of prevention with lifestyle modification. It is necessary to decide an appropriate time horizon by which to model interventions - if short term modelling is carried out, concurrent with the trial, it might result in an underestimation of QALYs (Latimer, 2011). While long term modelling (+20 years) is preferable it requires discounting so as not to give skewed results and many studies did not discount, but this is necessary especially where the benefits of prevention occur over a long time period. Where discounting

did occur, the rates varied between 3-7%, though most UK studies applied a discount of 3.5% as per the guidelines. One expert stated, '*there is no standard time to measure cost-effectiveness – it depends on the intervention*' (ID10).

Another important aspect of analysis is modelling. The modelling types varied by study; 60% of studies used a Markov model, 11% used a microsimulation model and the remaining studies used another method. Modelling is particularly important when we want to report the impact of prevention strategies where long-term benefits might not be immediate. Demonstrating the value of prevention might take time, whereas treating disease has an immediate effect on health and the economy. Also, governments or payers might be hesitant to pay in advance for programmes that will only show their effect in the future. All of the experts agreed that modelling, in particular Markov modelling, was a useful tool in cost-effectiveness analysis. However, modelling too far into the future has limitations and is less accurate. Different modelling techniques are likely to have different underlying assumptions.

Few studies made a direct comparison between an individual-based and population based measures. While there are good quality data available for the economic evaluation of drug treatments before they are recommended by the health services, this might not be the case for population level interventions where the costs and benefits may be accrued well beyond the health service. Comparison of public health interventions alongside treatment interventions modelled within the study is a useful point of future work.

Standardising terminology is important. Very often different terminology was used to describe the cost-effectiveness method. For example, authors often describe carrying out cost-effectiveness analysis but in fact have carried out cost-utility analysis with QALYs as an outcome. This view also emerged from the expert interviews (this was expressed by ID4 for NCDs I think CUA with QALY because interventions that target risk factors of coronary diseases they can potentially affect both the length of life and the QoL').

There were differences in the methods used between cost effectiveness studies of prevention, screening and treatment interventions. While it was still the most popular discount rate for each intervention type, many more screening interventions used the 3% discount rate (72%) compared with prevention (46%) and screening (47%) interventions. This appears to be due to the fact that most of the cost-effectiveness studies focusing on treatment interventions were conducted in countries where a 3% discount rate is used, such as the USA. Screening interventions were also more likely to have used the

healthcare perspective (84%) in comparison to prevention (72%) and management (65%). Due to the large scale of effects of prevention and screening interventions, and a lack of agreement on methodology, it may be that screening and prevention cost-effectiveness studies are more inclined to use the healthcare perspective. Markov modelling was used proportionally more in treatment interventions (74%) than in prevention (55%) or screening (60%). Prevention and screening studies may have to rely on more sophisticated models, as they often simulate an entire population. Finally, compared with screening (92%) and treatment (94%), economic evaluations of preventative interventions used the QALY less frequently as an outcome measure (70%), instead favoring DALYs, LYG and other outcomes. This may be due to relative popularity of the DALY in public health compared to other disciplines.

One notable trend was studies sponsored by pharmaceutical companies finding that recently launched drugs, such as statins and ACE inhibitors, were cost-effective when compared with the relevant generic. For example, the study by Barrios *et al* (CH10)(79) finds the statin rosuvastatin to be cost-effective compared to the generic atorvastatin. This study was funded by AstraZeneca, the company that owns the patent for rosuvastatin. A similar collaboration between the writers and the owners of the intervention also exists in numerous other studies including CH11, CH12, CH16 and CH26 (70;71;74;86). A consequence of this trend may be a shortage of cost-effectiveness studies for prevention or screening interventions compared to drug treatment, because of a lack of interest groups (or funding) pushing for research and publication.

Due to the use of country-specific factors, the transferability and comparability of cost-effectiveness studies between settings is difficult. Using the BENESCO model, Vemer and Rutten-van Mölken identify a number of factors that influence the cost-effectiveness outcomes of pharmacological smoking cessation therapies (SCTs) between 6 European countries. The discount rate used was found to have the largest overall impact on the ICER of the intervention. Higher discount rates for effects and costs resulted in a less favourable ICER, as the future QALY gains and cost-savings were worth less. For example, a given INMB for a SCT calculated using the Dutch-specific input parameters (using a 4% and 1.5% discount rate for costs and effects respectively), decreases by 65.2% when using the German discount rate of 5% for both costs and effects. The epidemiology of the disease related to the intervention had the second largest overall effect on cost-effectiveness; where the incidence rate is lower, the QALYs fall and the ICER worsens. Compared to the Dutch reference case, using the lower French incidence and mortality of smoking-related diseases reduces the INMB by 43.2%. Other important factors include the utility weights used and the resource use of the intervention. These findings suggest that the cost-

effectiveness results of a study based in one country may not apply to another, and strengthen the case for developing an international standardizing framework for economic evaluations.

In sum, it is difficult to compare the results of one cost-effectiveness analysis with another because of differences in healthcare systems, the use of comparator, types of methods used, types of costs included (direct or indirect), outcome measures used (e.g. QALYS, LYG), the discount rates used, the epidemiology of the disease and population groups. A framework from which to best approach for cost-effectiveness analysis should be developed.

Abbreviations

BMI - body mass index

CBA - cost-benefit analysis

CEA - cost-effectiveness analysis

CKD - chronic kidney disease

COPD - chronic obstructive pulmonary disease

CUA - cost-utility analysis

CVD - cardiovascular disease

DALYs - disability adjusted life years

DPP - Diabetes prevention programme

GFR - glomerular filtration rate

HD - hemodialysis

ICER - incremental cost-effectiveness ratio

IFG - impaired fasting glucose

IGT - impaired glucose tolerance

INMB – incremental net monetary benefit

KDOQI - Kidney Disease Outcomes Quality Initiative

NCDs - non-communicable diseases

NICE - National Institute for Health and Care Excellence

OECD - Organization for economic co-operation and development

QALYs - quality adjusted life years

RR - relative risk

T1D - type 1 diabetes

T2D - type 2 diabetes

UK - United Kingdom

USA - United States of America

WHO - World Health Organization

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