Medical-economical aspects of high sensitivity C-reactive protein assay for the prediction of coronary heart disease.
An analysis in Germany and Italy

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Key words:
Coronary heart disease; Cost-effectiveness; High sensitivity C-reactive protein; Primary prevention; Secondary prevention.

Background. **Elevated plasma concentrations of C-reactive protein (CRP) are associated with increased cardiovascular risk. We studied the cost-effectiveness of CRP determination in primary and secondary prevention settings in two European countries: Germany and Italy.**

Methods. **Using a decision analytic model we evaluated the costs and consequences of testing or not testing using a high sensitivity (hs)-CRP assay. In a primary prevention model we analyzed a hypothetical cohort of 300 000 apparently healthy men divided into three age groups (35-44, 45-54 and 55-64 years). Individuals with CRP levels > 3 mg/l were administered either aspirin or statins according to lipid levels. The cohort was followed for 5 years. In the secondary prevention model hs-CRP testing was evaluated in a cohort of 10 000 patients with total cholesterol levels < 4.52 mmol/l and a history of myocardial infarction or unstable angina. The two strategies tested were: 1) administer pravastatin only to those with high CRP values, and 2) treat all patients. The analysis was performed from the societal perspective. Event rates were obtained from epidemiological studies and clinical trials.**

Results. **In the primary prevention model, strategies including testing showed, for men aged 45 years and older, cost-effectiveness ratios between each life year saved (LYS) and cost savings in Germany equal to 10 217€ and between each LYS and savings in Italy equal to 16 950€ In the age group 35-44 years, therapy with aspirin showed cost-effectiveness ratios of 5318€ and 11 203€ per LYS in Germany and in Italy respectively. The widespread use of statins showed an unfavorable cost-effectiveness profile: 44 630€ per LYS in Germany and 36 270€ per LYS in Italy. In the secondary prevention model, hs-testing for CRP can reduce the cost-effectiveness of pravastatin from 16 400 to 6830€ per quality adjusted life year gained. Sensitivity analysis performed on the variables test price and costs of cardiovascular events resulted in minimal changes of the cost-effectiveness ratios.**

Conclusions. **Both in the primary and the secondary prevention settings, hs-testing for CRP can better target individuals at higher risk, thus improving outcomes and resulting in a more cost-effective strategy.**

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Introduction

Clinically overt coronary disease is the most common cause of death in Europe and the United States as well as in other industrialized countries[1]. It has been estimated that in these countries, coronary heart disease (CHD) accounts for 7.9% of the total health care expenditure. The largest share of direct costs is due to hospitalization, whereas productivity losses are the main component of indirect costs[2].

Health education and statutory measures to improve health-related behavior by the entire population are fundamental aspects of prevention. This approach is, however, not always enough and clinicians should focus on the identification and treatment of persons who are at increased cardiovascular risk (the individual or high risk strategy). Promotion of a healthy lifestyle will not only result in decreased CHD-related mortality and morbidity but also in a reduction in mortality and morbidity due to other causes. However, interventions that imply the use of therapeutic agents should be targeted to those individuals who would benefit most. The prediction of risk in individuals and populations is the ultimate goal of clinical-epidemiological research. Risk prediction at the individual level is still not satisfactory. Analyses based on data collected in the

Framingham Heart Study showed that, with regard to the 10-year CHD incidence, the predictive value of a single total cholesterol measurement has a sensitivity of 47% and a specificity of 76%[3]. When the total/HDL cholesterol ratio was used the sensitivity increased. When data analysis included all major risk factors (age, total and HDL cholesterol, blood pressure, smoking and diabetes), the sensitivity reached 70%, and the specificity 82%. This shows that the predictive power increases when all major risk factors are used for CHD prediction, but that there is still room for improvement[3].

The recent use of high sensitivity C-reactive protein (hs-CRP) assays in a large prospective study in patients with angina pectoris[4] and in three nested case-control studies in initially healthy subjects[5-7] showed a consistent positive association between baseline CRP levels and cardiovascular endpoints. In other studies, the strength of the association between CRP levels and future coronary events has also been shown[5,6,8]. In all these studies the relative risk of coronary events was increased 2 to 3 fold when top and bottom quartiles or quintiles of the CRP distribution were compared. Despite the association of CRP with other cardiovascular risk factors, multivariate analysis clearly showed an independent contribution of CRP in the prediction of future coronary events[9].

The aim of this study was to evaluate the medical-economical implications of using hs-CRP testing as a screening tool for risk stratification and consequent drug therapy in CHD in primary and in secondary prevention in two European countries: Italy and Germany.

Methods

Using analytic decision techniques[10], we created two models: one for primary prevention and the other for secondary prevention of cardiovascular disease. In these models we compared the costs and benefits of hs-CRP testing vs no testing. As testing alone will not reduce the cardiovascular risk, we assumed that, once individuals at increased risk are identified, some therapeutic intervention will be undertaken. In the primary prevention model men with CRP values ≥ 3 mg/l (proposed cut-off point) were given either aspirin or statins; in the secondary prevention model (assuming that most patients with a history of cardiovascular disease are already on aspirin) the intervention consisted only in the prescription of statins.

The time limit of the models was 5 years. A societal perspective was used. Indirect costs, however, were not considered, as available data regarding this parameter were not sufficient.

Primary prevention model. For each country the costs and consequences of hs-CRP testing were calculated in the primary prevention model for three cohorts of 100 000 men each: one aged 35 to 44, one aged 45 to 54 and one aged 55 to 64 years. Similar to what had been done in the National Health and Nutrition Examination Survey[11], each cohort was divided, according to serum total cholesterol and low density lipoprotein (LDL) levels, into three other cohorts: one including individuals having high lipid levels (total cholesterol > 7.8 mmol/l or LDL > 4.9 mmol/l), one including subjects with borderline lipid levels (total cholesterol between 5.11 and 7.8 mmol/l or LDL between 4.11 and 4.90 mmol/l) and one, persons with desirable lipid levels (total cholesterol < 5.11 mmol/l or LDL < 4.11 mmol/l). Prevalence data on cholesterol levels among European adults were obtained from the Seven Countries Study[12,13] and other studies[14-16]. Subjects with borderline lipid levels were further divided into those with two or more risk factors and those with less than two risk factors. Risk factors have been described elsewhere[17]. Men with high lipid levels and those with borderline lipid levels and two or more risk factors were considered to be on statins according to recommendations of international published guidelines[18].

Probabilities of cardiovascular events over 5 years were calculated for each group using published epidemiological data from several primary prevention studies (Physician's Health Study[19], West of Scotland Coronary Prevention Study[20], Multiple Risk Factor Intervention Trial[5,21], Helsinki Heart Study[22,23] and fitted for Italy and Germany using age, gender and disease specific mortality data from each country[24]. When an event occurred, the probability that it was a CHD death was considered to be 0.15, the probability that it was a non-fatal myocardial infarction 0.50 and that of being another cardiovascular event 0.35. Cardiovascular events were defined as follows: cardiovascular disease death: death from CHD or fatal myocardial infarction or fatal ischemic stroke; myocardial infarction: non-fatal myocardial infarction; other cardiovascular events: unstable angina or severe stable angina requiring arteriography, percutaneous transluminal coronary angioplasty or coronary artery bypass grafting and non-fatal ischemic stroke.

Age and gender specific mortality rates for cardiovascular disease for each country were obtained from the WHO Statistical Information Website[24] and are shown in table I.

Three strategies were considered: strategy A represents the actual situation in which the test to determine CRP status is not performed, and the therapeutic decision to prescribe cholesterol-lowering drug treatment is based on lipid levels and the presence or absence of other risk factors; in strategies B and C the test to determine CRP levels was performed every 2 years. Patients who, regardless of their CRP status, qualify for cholesterol-lowering therapy (all those in strategy A who qualify for such treatment) were further considered to receive statins. In strategy B, men with CRP serum levels > 3 mg/l (further called CRP positive), borderline lipid levels and less than two other risk factors were considered

Table I. Mortality rates for cardiovascular disease and life expectancy among men according to age in Germany and Italy (1996).

Age group	Germany		Italy	
	Mortality/10^5	Life expectancy	Mortality/10^5	Life expectancy
35-44	28	35.9 years at age 40	22.2	37.3 years at age 40
45-54	132	27.6 years at age 50	94	28.5 years at age 50
55-64	330	18.8 years at age 60	250.6	19.6 years at age 60

to be on treatment using statins; CRP positive individuals with LDL titers < 4.11 mmol/l or total cholesterol levels < 5.11 mmol/l (desirable lipid levels) were considered as being on aspirin. In strategy C both groups were considered as being on aspirin. In those with CRP values ≥ 3 mg/l, aspirin was considered to reduce the relative risk of cardiovascular events by 60%[6] and statins by 80%[25]. Prevalence data on CRP serum levels in the European general population are based on a personal communication (Kluft C., Leiden, The Netherlands) and were discussed with a panel of experts. In the age group including subjects 35-44 years old, 10% were considered to have serum levels ≥ 3 mg/l, in the age group including individuals 45-54 years old, 20% and in the age group including subjects 55-64 years old a prevalence of 30% was assumed.

Type of analysis. For the primary prevention model a cost-effectiveness analysis was performed. Incremental costs (the difference in costs between the two alternatives) were compared to the incremental outcomes (difference in outcomes between the two alternatives) as measured in natural units. Because primary prevention is directed to apparently healthy individuals, the natural unit used was life years saved (LYS) obtained by multiplication of the number of deaths averted by the life expectancy at the middle age of the cohort. Life expectancy data for each country and cohort were obtained from OECD Health Data 2000[26] and are shown in table II.

Secondary prevention model. For the secondary prevention model we considered only patients with a history of myocardial infarction and average lipid levels (total cholesterol < 4.52 mmol/l). This setting was identical to that of the Cholesterol and Recurrent Events (CARE) trial[27]. Probabilities of an event or no event were also derived from this study. A detailed description of the CARE study has been given elsewhere. In brief, the CARE trial recruited 4159 patients (3583 men and 576 women) with myocardial infarction who had plasma cholesterol levels < 4.52 mmol/l. In this double-blind trial lasting 5 years, patients were administered either 40 mg of pravastatin per day or placebo. The primary endpoint was either a fatal coronary event or a non-fatal myocardial infarction. According to Ridker et al.[25,28], patients with pre-randomization CRP levels in the highest quintile (> 6.6 mg/l) had a relative risk of developing recurrent disease 75% higher than those in the lowest quintile (for CRP relative risk 1.77). In case of pravastatin treatment, the association between high CRP levels and the risk of CHD was attenuated (odds ratio 1.2 and not significant). Among those with evidence of inflammation, the proportion of recurrent events prevented by pravastatin was 54% compared with 25% among those without inflammation in spite of virtually identical baseline levels of total cholesterol, LDL and triglycerides.

We studied the costs and consequences over 5 years of hs-CRP testing in a cohort of 10 000 patients with the same characteristics as those in the CARE study. Two strategies were explored: in strategy I the test was not performed and all patients were given pravastatin. In strategy II the test was performed every 6 months and only those with high CRP levels were given pravastatin. The prevalence of high CRP levels in the study population was 40%[25].

Type of analysis. In the secondary prevention setting a cost-utility analysis was performed. Cost-utility refers to a particular type of cost-effectiveness analysis where outcomes are measured in terms of quality adjusted life years (QALY) gained[29]. QALYs combine quantitative and qualitative changes in life into one composite mea-

Table II. Life years saved (LYS) (number of deaths averted * life expectancy at that age) over a 5-year period according to the strategy in primary prevention.

Age group	Germany		Italy	
	Strategy B	Strategy C	Strategy B	Strategy C
35-44	431 LYS	287 LYS	485 LYS	224 LYS
45-54	3367 LYS	2926 LYS	3078 LYS	2629 LYS
55-64	5640 LYS	4324 LYS	5449 LYS	4018 LYS

sure. Quality adjustment factors reflect aggregated preferences of individuals for the outcomes. Recurrent events in patients with a history of myocardial infarction will not only increase the risk of death but also negatively influence the quality of life.

The life expectancy for patients with a mean age of 55 years and a history of myocardial infarction was estimated to be 13.6 years and the quality adjustment factor was considered to be 0.85 for myocardial infarction and 0.90 for other cardiovascular events.

Estimating health care costs. Costs from the societal perspective have been calculated from published data[30-32] and completed by expert opinion. The cost of CRP testing was estimated to be 4 times that of the sale price of the test (Dade Behring, personal communication). This represents 3.80€ for Germany and 7.50€ for Italy. Statin treatment was priced at 870€ in Germany (according to prices published in the Rote List Internet) and at 830€ in Italy per patient-year of treatment. Aspirin was priced at 23€ in Germany and at 20€ in Italy per patient-year of treatment. For Germany, a cardiovascular death was valued at 3730€, a myocardial infarction (inclusive of follow-up costs) at 15 300€ and other cardiovascular events at 4700€. The corresponding prices for Italy were 2580€, 11 400€ and 3890€ respectively.

Sensitivity analysis. In order to test the robustness of our conclusions, a sensitivity analysis was performed on the price of the test and on the costs of the cardiovascular events. Especially because the price of the test is an estimate, we explored the consequences that a much higher price (even 2 times higher) would have on our results.

Results

Primary prevention. As shown in figure 1, the cost of testing for CRP in the primary prevention setting represents only a modest sum compared with the high economic burden of cardiovascular disease. Testing, however, is only meaningful if followed by an intervention. We have explored two possibilities of intervention: in strategy B, all patients with CRP serum levels ≥ 3 mg/l and with borderline serum lipid levels were administered a statin, while those with desirable lipid levels were given aspirin. In strategy C, only those with two or more risk factors received a statin (usual care) whereas the others received aspirin.

Tables III and IV show the cumulative number of cardiovascular events over 5 years resulting from the intervention in Italy and Germany respectively. A 7-12% reduction in the number of cardiovascular events in the cohort aged 35-44 years can be achieved. Because of the low prevalence of CRP serum values > 3 mg/l and the low probability of events in this age group, the cost-effectiveness of the strategy using statin in all men with borderline lipid levels is less favorable (44 630€ per LYS for Germany and 36 270€ per LYS in Italy). This also

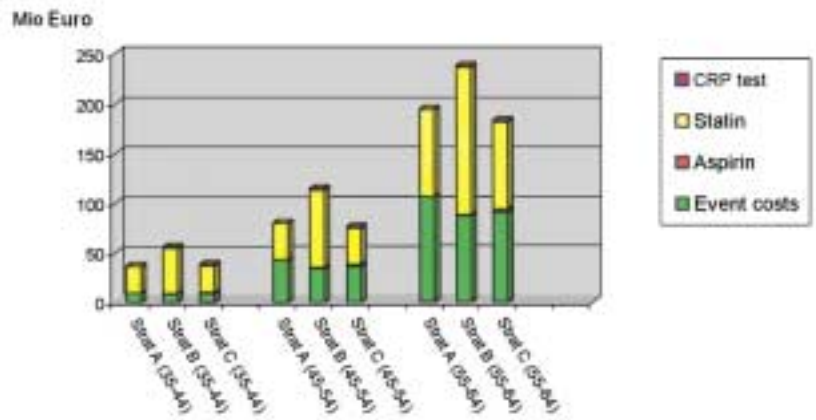

Figure 1. *Comparison, according to strategy, of expected expenditures over 5 years for the different cohorts in Germany in millions of €. CRP = C-reactive protein.*

Table III. Total number of cardiovascular events over 5 years in a cohort of 300 000 German men according to age in the primary prevention model.

Age of the cohort	Strategy A (usual care)	Strategy B	Strategy C	Reduction in % Strategy B	Reduction in % Strategy C
35-44	934	842	882	-12	-7
45-54	4400	3483	3690	-18	-14.5
55-64	11 000	9000	9440	-21	-16.2

Table IV. Total number of cardiovascular events over 5 years in a cohort of 300 000 Italian men according to age in the primary prevention model.

Age of the cohort	Strategy A (usual care)	Strategy B	Strategy C	Reduction in % Strategy B	Reduction in % Strategy C
35-44	740	658	699	-11.7	-6.30
45-54	3134	2414	2629	-18.3	-14.5
55-64	8351	6500	6986	-22.2	-16.3

applies for the cohorts aged 45-54 and 55-64 years. In the cohort aged 45-54 years, reductions in cardiovascular events equaling 18 and 14.5% were achieved with strategies B and C respectively. In the cohort aged 55-64 years, the reductions were 21 and 16.3% respectively. These higher values were due to the increased prevalence of CRP serum levels ≥ 3 mg/l in this age group.

Figure 1 shows the total costs, in millions of €, according to the strategy used in Germany and figure 2 the corresponding expenditures in Italy. In all cohorts, more widespread treatment using statins (i.e. strategy B) resulted in a higher effectiveness but also in increased costs. In both countries the number of deaths and of cardiovascular events averted increased with the age of the cohort and this fact is reflected in a more favorable cost-effectiveness profile (Table V).

In strategy C (that restricts statins to those with high serum lipid levels and those with borderline lipid levels and two or more risk factors) savings have been achieved for the cohorts aged 45-54 and 55-64 years. The younger cohort studied (aged 35-44 years) showed in this strategy a very favorable cost-effectiveness profile: 5318€ per LYS in Germany and 11 203€ per LYS in Italy.

Results of the sensitivity analysis are shown in tables VI and VII. Because the price of testing the whole cohort (0.95 million € in Germany and 1.88 million € in Italy) is less than 2% of the event costs in the cohort aged 45-54 years and even less than 1% in the cohort aged 55-64 years in Germany, the cost-effectiveness ratios remain favorable even if the price of the test were 2 times the one estimated.

Secondary prevention. Table VIII shows the number of events expected over 5 years in a cohort of patients with a history of myocardial infarction or unstable angi-

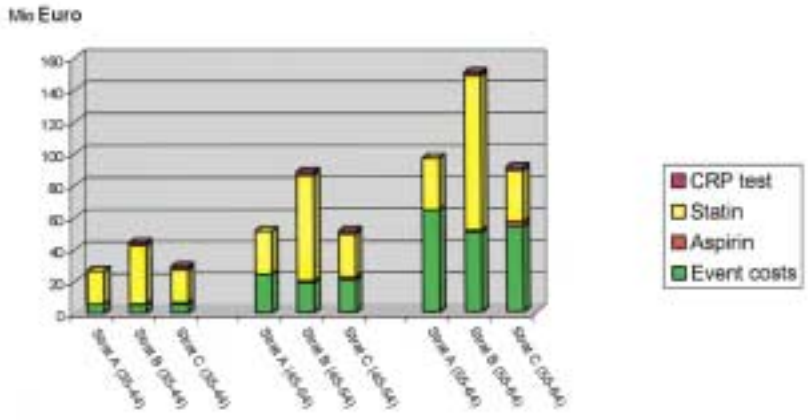

Figure 2. *Comparison, according to strategy, of expected expenditures over 5 years for the different cohorts in Italy in millions of €. CRP = C-reactive protein.*

Table V. Cost-effectiveness of both strategies with testing (strategies B and C) vs no testing (strategy A) in Germany and Italy according to the cohort.

Cohort	Germany		Italy	
	Strategy B	Strategy C	Strategy B	Strategy C
35-44	44 630€/LYS	5318€/LYS	36 270€/LYS	11 203€/LYS
45-54	10 217€/LYS	Cost saving	16 950€/LYS	Cost saving
55-64	7760€/LYS	Cost saving	9905€/LYS	Cost saving

LYS = life years saved.

Table VI. Sensitivity analysis of the incremental cost-effectiveness ratios (expressed in € per life year saved) of strategies B and C vs strategy A in Italy.

Cohort	Price of the test				Price of the cardiovascular events			
	50% higher		100% higher		30% higher		30% lower	
	Strategy B	Strategy C	Strategy B	Strategy C	Strategy B	Strategy C	Strategy B	Strategy C
35-44	45 675	6885	46 770	8540	44 014	4795	45 246	5841
45-54	10 350	CS	10 452	CS	9429	CS	11 004	CS
55-64	7840	CS	7924	CS	6736	CS	8785	CS

CS = cost saving strategy.

Table VII. Sensitivity analysis of the incremental cost-effectiveness ratios (expressed in € per life year saved) of strategies B and C vs strategy A in Germany.

Cohort	Price of the test				Price of the cardiovascular events			
	50% higher		100% higher		30% higher		30% lower	
	Strategy B	Strategy C	Strategy B	Strategy C	Strategy B	Strategy C	Strategy B	Strategy C
35-44	38 200	15 392	40 139	19 581	35 885	10 777	36 660	11 629
45-54	12 232	375	12 536	807	11 390	CS	12 464	478
55-64	10 077	CS	10 249	CS	9126	CS	10 684	CS

CS = cost saving strategy.

Table VIII. Number of cardiovascular events over 5 years in a cohort of 10 000 patients with a history of myocardial infarction and "high" C-reactive protein serum levels.

	Placebo	Pravastatin after testing
Cardiovascular death	580	420
Myocardial Infarction	1125	832
Other	1705	1290

na and with CRP serum values > 3 mg/l with and without administration of pravastatin. The cost-utility ratios of administering pravastatin to all patients (strategy I) or else on the basis of CRP determinations (strategy II) are shown in table IX for Germany and Italy. By targeting patients with the highest risk of recurrent events, CRP determination allows a far better cost-effectiveness ratio.

Discussion

The addition of hs-CRP assay to lipid level determination has been shown to result in a significant improvement in the ability to predict risk compared to that already achievable through the use of established cardiovascular risk factors. Furthermore, it can improve the effectiveness of currently available therapies by selecting patients at higher risk. Baseline CRP concentrations, determined at high sensitivity assay, seem to modulate the efficacy of two preventive therapies: low-dose aspirin and 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins)[33]. Data from double-blind, randomized clinical trials suggest that the relative efficacy of these two commonly used therapies may be greater in persons with evidence of underlying inflammation as assessed by hs-CRP assay[6,25].

Table IX. Incremental cost-effectiveness ratios of treatment with pravastatin in the secondary prevention without (strategy I) and with (strategy II) C-reactive protein determination vs no treatment.

Germany		Italy	
Strategy I	Strategy II	Strategy I	Strategy II
16 397€/QALY	6123€/QALY	16 417€/QALY	6830€/QALY

QALY = quality adjusted life year.

Aspirin has been evaluated in primary prevention trials, but is not currently recommended in primary prevention because of the concerns regarding the risk of increased bleeding[34]. Hs-CRP determination, however, improves the benefit-to-risk ratio in apparently healthy persons and constitutes in our model a cost saving strategy in the cohorts aged 45 to 54 and 55 to 64 years in both countries.

HMG-CoA reductase inhibitors (statins) have been shown to reduce mortality and morbidity both in the primary as well as in the secondary prevention of cardiovascular disease[20,27,35-37]. Several economic evaluations regarding statins have been performed[38-43]. Cost-effectiveness ratios vary greatly (a good overview of the pharmacoeconomics of lipid-lowering agents may be found in the article by Hay et al.[44]). Most authors however, agree that the estimated cost per life-year saved mostly depends on the patient-risk profile. Cost-effectiveness ratios in fact correlate with the number of patients needing treatment. In our model, the most cost-effective strategies were those targeting men over 45 and the one including CRP determination in secondary prevention. In the comparison of the two European countries, Germany, with a higher incidence of cardiovascular disease, shows a better cost-effectiveness profile than Italy.

We have based our model on several assumptions that have to be confirmed by more extensive epidemiological and medical-economical research. Models are a way of representing the complexity of the real world in a more simple and comprehensive form. In health economic evaluations, models are typically used where the relevant clinical trials have not been conducted or did not include economic data capture. The main disadvantage of decision analytic modeling is that various pieces of information from different studies and populations are put together into the same model[45]. The main advantage is a timely and flexible framework for analysis. Transfer of new technologies such as hs-CRP testing, requires clinical and cost-effectiveness evaluation in order to optimize the quality and efficiency of health care.

The two main limitations of our study are: first, some of the assumptions made have to be confirmed by more extensive epidemiological and clinical research. This regards the prevalence of CRP values > 3 mg/l among apparently healthy European adults and the differential effectiveness of prevention with aspirin and statins. Our estimations are based on the effectiveness calculated in nested case-control studies. The second main limitation is that we have not explored the cost effectiveness in women and in the elderly. However, it is in the elderly that an exponential increase in the incidence of cardiovascular events is expected.

This study shows however, that CRP is a cost-effective marker which improves the prediction of the increased risk of cardiovascular disease especially among individuals aged 45 years and older. Furthermore, it can improve the effectiveness of currently available therapies by selecting patients at higher risk. Both in the primary and in the secondary prevention settings, testing for CRP can be a powerful tool in the control of health care costs.

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