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Cholesterol-lowering drugs: science and marketing

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Summary

Long-term use of statin therapy is essential to obtain clinical benefits, but adherence is often suboptimal and some patients are also reported to fail because of 'statin resistance'. The identification of PCSK9 as a key factor in the LDL clearance pathway has led to the development of new monoclonal antibodies. Here we critically review the economic evaluations published in Europe and focused on statins. We searched the PubMed database to select the studies published from July 2006 to June 2016 and finally selected 19 articles. Overall, the majority of studies were conducted from a third-party payer's viewpoint and recurred to modelling. Most studies were sponsored by industry and funding seemed to play a pivotal role in the study design. Patients resistant to LDL-C level reduction were considered only in a few studies. The place in therapy of the new class of biologic should be considered a kind of 'third line' for cholesterol-lowering, after patients have failed with restricted dietary regimens and then with current drug therapies. Otherwise they could result in hardly sustainable expenses even for developed countries.

Keywords

cardiovascular medicine, drugs, health economics, health policy

Introduction

Cardiovascular disease is the main cause of death in Europe and worldwide.[1,2] The relationship between low-density lipoprotein cholesterol levels and cardiovascular disease is well recognised and understood.[3,4] In view of the key role of low-density lipoprotein cholesterol in the atherosclerotic process, cholesterol-lowering therapy represents one of the established tools for reducing cardiovascular risk in both primary and secondary prevention.[5]

The current cholesterol-lowering drugs include statins, bile acid sequestrants and selective cholesterol absorption inhibitors.[6] Since their introduction, statins have become a cornerstone for cardiovascular disease prevention, with demonstrated efficacy in reducing cardiovascular morbidity and mortality in both primary and secondary prevention, particularly in high-risk patients.[7–9]

Long-term use is essential to obtain clinical benefits but adherence to statin therapy is often suboptimal, for various reasons (e.g. patient's age, sex and polypharmacy) besides adverse effects,[10,11] which can all contribute to failure in low-density lipoprotein cholesterol levels.[12] Yet, some patients are reported to fail in achieving low-density lipoprotein cholesterol targets because of 'statin resistance',[13] a condition associated with both genetic and environmental factors (such as gene polymorphisms and smoking) as well as pathological states (e.g. inflammation, hypertension and HIV infection).

The identification of proprotein convertase subtilisin/kexin type 9 (PCSK9),[14] a key factor in the LDL clearance pathway, and the finding that individuals with loss-of-function mutations in PCSK9 have low plasma levels of low-density lipoprotein cholesterol[15] and are protected from coronary heart disease[16] have led to the development of new therapeutic options aimed at PCSK9 inhibition. Evolocumab and alirocumab (both monoclonal antibodies against PCSK9)[17,18] have now been approved for patients with mixed dyslipidaemia, heterozygous (familial and non-familial) and homozygous familial hypercholesterolaemia. Both biologics should be prescribed: (i) in combination with a statin only or a statin with other lipid-lowering therapies in patients unable to reach low-density lipoprotein cholesterol goals with the maximum tolerated dose of a statin; and (ii) alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant (or for whom a statin is contraindicated). A third antibody (bococizumab) is currently in phase III trials for similar indications,[19] with likely to gain market approval in late 2016. All antibodies are injected subcutaneously once/twice per month.

Here, we critically review the full economic evaluations published in Europe and focused on statins and assess whether and how these studies included in their analyses the patients resistant to low-density lipoprotein cholesterol level reduction despite statin treatment, who are ideally the main therapeutic target for the new anticholesterol monoclonal antibodies. Finally, we discuss the potential future scenarios for

Table 1. Main characteristics of the selected studies.

First author, year, setting	Type of study, perspective	Therapeutic target	Alternatives	Model, time horizon (discount)	Cost items	Therapy adherence	Main conclusion	Sponsorship	Therapy resistance
Becerra, 2015, UK[20]	Cost-utility analysis third-party payer	Secondary cardiovascular disease prevention	Fixed-dose combination polypill (aspirin, atorvastatin and ramipril) vs. multiple monotherapy	Markov, lifetime (3.5% costs and outcomes)	Drugs Cardiovascular disease events and death Hospitalisations Surgical procedures	Yes	The polypill strategy appears to be cost-effective	Yes	No
McConnachie, 2013, UK[21]	Cost-utility analysis third-party payer	Primary cardiovascular disease prevention	Pravastatin vs. placebo	Cox proportional hazards, 15 years (3.5% costs and outcomes)	Drugs Medical and nurse visits Monitoring and laboratory tests	No	Pravastatin treatment is cost saving and increases QALYs in middle-aged men	Yes	No
Barrios, 2012, Spain[22]	Cost-utility analysis third-party payer	Primary and secondary cardiovascular disease prevention	Rosuvastatin vs. generic atorvastatin	Markov, 20 years (3% costs and outcomes)	Drugs Hospitalisation and follow-up	No	Rosuvastatin is more cost-effective than generic atorvastatin	Yes	No
Liew, 2012, Belgium[23]	Cost-utility analysis third-party payer	Primary cardiovascular disease prevention	Remaining on atorvastatin vs. switching to simvastatin	Markov, 20 years (3% costs, 1.5% outcomes)	Drugs Hospitalisation and follow-up	No	Remaining on atorvastatin should be costeffective	Yes	No
Ohsfeldt, 2012, Sweden[24]	Cost-utility analysis third-party payer	Primary cardiovascular disease prevention	Rosuvastatin vs. placebo	Probabilistic Monte Carlo, lifetime (3% costs and outcomes)	Drugs Medical visits Monitoring tests Hospitalisations	Yes	Rosuvastatin is cost-saving in patients with 10-year risk of cardiovascular disease events	Yes	No
Michailov, 2012, Germany[25]	Cost-utility analysis third-party payer	Secondary cardiovascular disease prevention	Simvastatin plus niacin/laropiprant vs. simvastatin	Markov, lifetime (3% costs and outcomes)	Drugs Medical visits Laboratory tests cardiovascular disease events and deaths	No	Addition of niacin/laropiprant to simvastatin is cost-effective in patients not at low-density lipoprotein cholesterol goal	Yes	Yes
Ara, 2012, UK[26]	Cost-utility analysis third-party payer	Patient with acute coronary syndrome	Atorvastatin 80 mg / rosuvastatin 40 mg vs. simvastatin 40 mg	Markov, lifetime (3.5% costs and outcomes)	Drugs Medical visits Laboratory tests Cardiovascular disease events and follow-up	Yes	Rosuvastatin 40 mg is estimated to be more cost-effective	No	No
Greving, 2011, NL[27]	Cost-utility analysis third-party payer	Primary cardiovascular disease prevention	Low-dose statin vs. no treatment	Markov, 10 years (4% costs, 1.5% outcomes)	Drugs Medical visits Pharmacists' fees Laboratory tests	Yes	Statins seem not to be cost-effective for primary prevention in patients at low risk	No	No

(continued)

Table 1. Continued.

First author, year, setting	Type of study, perspective	Therapeutic target	Alternatives	Model, time horizon (discount)	Cost items	Therapy adherence	Main conclusion	Sponsorship	Therapy resistance
					Cardiovascular disease events, follow-up and death				
Plans-Rubió, 2010, Spain[28]	Cost-effectiveness analysis third-party payer	Primary cardiovascular disease prevention	Atorvastatin/fluvastatin/ lovastatin/pravastatin/ rosuvastatin/ simvastatin vs. no treatment Statin + cholestyramine/ ezetimibe vs. no treatment	Metanalysis for efficacy, 1 year	Drugs Medical visits Laboratory tests Adverse effects	No	Rosuvastatin should be cost-effective for patients with high risk, but combination therapies for greater reductions in low-density lipoprotein cholesterol, and simvastatin for those with moderate or low CHD risk	No	Yes
Reckless, 2010, UK[29]	Cost-utility analysis third-party payer	Patients with acute coronary syndrome	Switching to simvastatin + ezetimibe vs. doubling submaximal statin doses	Markov, lifetime (3.5% costs and outcomes)	Drugs Medical visits Cardiovascular disease events, follow-up and death	No	Switching to simvastatin + ezetimibe is cost-effective	Yes	No
Lorgelly, 2010, UK[30]	Cost-effectiveness analysis third-party payer	Systolic heart failure	Rosuvastatin vs. placebo	Within trial analysis, 3 years (3.5% costs and outcomes)	Drugs Hospitalisations Surgical procedures	Yes	Rosuvastatin significantly reduces healthcare costs	Yes	No
Nherera, 2010, UK[31]	Cost-utility analysis third-party payer	Familial hypercholesterolaemia (FH)	High-intensive statins vs. low-intensive statins	Markov, lifetime (3.5% costs and outcomes)	Drugs Cardiovascular disease events and follow-up Surgical procedures	No	High-intensive statins are cost-effective for younger FH patients	No	No
Martikainen, 2010, Sweden[32]	Cost-effectiveness analysis third-party payer	High-risk patients with hypercholesterolaemia	Eight treatment strategies including high-intensive statins	Probabilistic decision tree, 1 year	Drugs Medical visits Laboratory tests Travelling	No	Rosuvastatin in high low-density lipoprotein cholesterol patients is cost-effective	Yes	Yes
Soini, 2010, Finland[33]	Cost-utility analysis Society	Secondary prevention of coronary heart disease	Simvastatin 40 mg/ atorvastatin 20 mg/ rosuvastatin 10 mg + ezetimibe 10 mg vs. simvastatin 40mg	Markov, lifetime (3% costs and outcomes)	Drugs Medical visits Monitoring and laboratory tests Hospitalisations Travelling	No	Switching to simvastatin + ezetimibe is cost-effective in patients not at goal	Yes	Yes

(continued)

Table 1. Continued.

First author, year, setting	Type of study, perspective	Therapeutic target	Alternatives	Model, time horizon (discount)	Cost items	Therapy adherence	Main conclusion	Sponsorship	Therapy resistance
Taylor, 2009, UK, Spain, Germany[34]	Cost-utility analysis third-party payer	Secondary cardiovascular disease prevention	Atorvastatin 80 mg vs. atorvastatin 10 mg	Markov, lifetime (3.5% costs and outcomes)	Drugs Cardiovascular disease events Surgical procedures	No	Atorvastatin 80 mg is cost-effective	Yes	No
Peura, 2008, Finland[35]	Cost-utility analysis third-party payer	Primary and secondary coronary heart disease prevention	Rosuvastatin/ vs. simvastatin	Markov, lifetime (5% costs and outcomes)	Drugs Medical visitsLaboratory tests Myocardial infarction events and death Travelling	No	Rosuvastatin can be considered potentially cost-effective	Yes	No
Gouveia Pinto, 2008, Portugal[36]	Cost-effectiveness analysis third-party payer	Hypercholesterolemia and prevention of ischemic heart disease	Rosuvastatin vs. atorvastatin/pravastatin/ simvastatin	Markov, lifetime (5% costs and outcomes)	Drugs Medical visits Laboratory tests Myocardial infarction events Examinations	Np	Rosuvastatin is a cost-effective alternative	Yes	No
Lindgren, 2007, Scandinavian countries[37]	Cost-effectiveness analysis, Cost-utility analysis Society	Secondary cardiovascular disease prevention	High-dose atorvastatin vs. regular dose simvastatin	Markov, lifetime (3% costs and outcomes)	Drugs Hospitalisations Surgical procedures Productivity loss	Np	High-dose atorvastatin appears to be cost-effective	Yes	No
Scuffham, 2006, Hungary[38]	Cost-effectiveness analysis, Cost-utility analysis third-party payer	Treatment after percutaneous coronary intervention	Fluvastatin vs. no treatment	Markov, 10 years (5% costs and outcomes)	Drugs Medical visits Cardiovascular disease deaths Hospitalisations	Yes	Fluvastatin is cost-effective	Yes	No

Box 1. Main results of the review on statins.

Methods	Thirteen studies included a cost-utility analysis,[20–27,29,31,33–35] four studies a cost-effectiveness analysis[28,30,32,36] and the remaining two both the techniques together.[37,38] Seventeen studies took a third-party payer's viewpoint,[20–32,34–36,38] only two a societal perspective[33,37] – one of them without including indirect costs.[30] Eleven of the 13 cost-utility analyses and one of the four cost-effectiveness analyses were based on Markov models[20,22,23,25–27,29,31,33–36] – such as the two studies including both the techniques[37,38] – while the remaining five[21,24,28,30,32] used other models. Eleven studies adopted a lifetime horizon,[20,24–26,29,31,33–37] five were designed over long-term periods[21–23,27,38] and only three were short-term.[28,30,32]
Costs	All the studies estimated the costs of drugs and management of cardiovascular disease events (hospitalisations, follow-up treatments and monitoring procedures). Five of the 19 included the costs of surgical interventions[20,30,31,34,37] and six of those related to death too;[20,25,27,29,35,38] three extended the estimates to direct non-healthcare costs (i.e. travel).[32,33,35] The Spanish study[28] was the only one that estimated the costs relating to adverse drug effects.
Funding	Fifteen studies were funded by industry and all concluded in favour of the sponsored products.[20–25,30,32–38] Three of the remaining studies concluded in favour of a statin treatment,[26,28,29] while the last – focused on patients at low risk in primary prevention – was the only one that was unfavourable.[27]
Statin resistance	Only four studies took account of resistance to statins. The German[25] and Finnish[33] cost-utility analyses in secondary prevention mainly differed in the efficacy sources (respectively, one short-term clinical trial and various clinical studies selected through a systematic literature search) and the single statins assessed (only simvastatin in the former, also atorvastatin and rosuvastatin in the latter). Both studies concluded in favour of an association of actives (simvastatin + niacin/laropiprant in the former, simvastatin + ezetimibe in the latter) – all drugs marketed by the (same) sponsor. In the Spanish cost-effectiveness analysis,[28] all statins and combinations with cholestyramine/ezetimibe were compared with no treatment in primary prevention, while the Swedish cost-effectiveness analysis[32] limited the comparison to eight different statin therapies for high-risk patients with hypercholesterolaemia. Both studies estimated the efficacy of therapies through a meta-analysis and concluded in favour of rosuvastatin (the sponsor's drug in the Swedish study), the Spanish study recommending combination therapies too when greater reductions in low-density lipoprotein cholesterol are required.

the 'market' of these new drugs from a third-party payer's perspective.

Methods

We searched the PubMed international database to select the full economic evaluations conducted in the European Union countries and focused on statins as cholesterol-lowering drugs. From the 198 articles published in English from July 2006 to June 2016 initially identified, we finally selected and screened 19 articles[20–38] (see Table 1 and Box 1).[a]

Results

The studies came from 11 European Union countries, more than half of them from Sweden (4) and the UK (6). Six studies focused on primary prevention,[21–24,27,28] five on secondary,[20,25,33,34,37] one on both[35] and the remaining seven on other therapeutic targets – three on subjects with hypercholesterolaemia[31,32,36] and four on patients affected by severe cardiovascular diseases.[26,29,30,38] Fifteen studies analysed therapies with statins alone,[20–27,30–32,34–38] four in combination with other active agents.[25,28,29,33] Only six of the 19 studies took account of statin therapy adherence,[20,24,26,27,30,38] five of the remaining 13 assumed that all patients were fully compliant,[25,29,32–34] while three did not mention adherence as an issue.[21,28,36]

Only four studies selected took into account the question of resistance to statins in their analyses.[25,28,32,33] One study focused on primary prevention,[28] two on secondary[25,33] and the remainder on high-risk patients for hypercholesterolaemia.[32] The two studies in secondary prevention,[25,33] based on lifetime Markov models, focused only on patients who failed to meet their low-density lipoprotein cholesterol target level with statin alone and analysed the additional benefit of combination therapies; the two others conducted a subgroup analysis over a one-year period in patients who did not achieve the low-density lipoprotein cholesterol therapeutic target.[28,32]

Overall, the majority of European full economic evaluations on statins were conducted from a third-party payer's viewpoint on therapeutic targets of demonstrated efficacy for these drugs, using modelling to estimate the cost-effectiveness of single statins, mostly over a long-term time horizon. Many studies included costs related to death, and some even direct non-healthcare costs in their estimates, but adherence to statin therapies was hardly considered, even though long-term therapy is essential to obtain clinical benefits. The majority of studies were sponsored by industry and funding seemed to play a pivotal role in the study design, with results aimed at supporting the cost-effectiveness of the sponsored drug, as is often the case in pharmaco-economic literature.[39]

Patients resistant to low-density lipoprotein cholesterol level reduction, i.e. the major therapeutic target of the new anticholesterol biologics, were considered only in a few studies. Yet, they were all conducted after the patent expiry of the first statins launched, and most analyses were extended to associations with other (in-patent) actives as alternatives, concluding in favour of either high-intensity statins or combination therapies.

With this background, we tend to conclude that statin resistance was not considered a relevant 'unmet need' in the European economic evaluations conducted before the launch of the new human antibodies.

Policy implications

At this stage, we wonder whether and how the forthcoming launch of this new class of biologics will affect the present market situation in the near future. In principle, these drugs should be prescribed for very specific patient targets, which represent 'market niches'. Although these new products are expected to be very costly (as is typical for new human antibodies), the whole 'budget impact' of this therapeutic class on pharmaceutical expenditure should be limited, as for any rare disease, even though they might be prescribed as add-on therapy, with consequent extra cost for third-party payers. Moreover, the subcutaneous injection of human antibodies can hardly be considered an advantage for patients' quality of life compared to a daily statin pill, although their marketers may well claim that the (bi)monthly schedules should facilitate patient adherence to cholesterol lowering therapy.

Following a rational strategy, the place in therapy of these new products could be considered a kind of 'third line' for cholesterol-lowering, after patients have failed with restricted dietary regimens first and then with current drug therapies (starting from statins) second.

However, experience in various other pathologies can lead us to predict very different scenarios, in which the role of the new antibodies may grow substantially depending on the marketing support that companies provide to promote them – as is typical in the (non) pharmaceutical market, where supply can often induce demand.[40] This is even more likely when the new products challenge off-patent drugs at the end of their 'life cycle', as happens in this competitive arena. A substantial 'switch' of prescribing patterns might lead to a massive budget impact for third-party payers, in line with the growth of the symptom in developed countries[41] and the increasing restrictions recommended in clinical guidelines.[6]

According to a rough estimate based on the first official prices issued in the UK, a year's treatment with the new human antibodies would cost around £4000 – at least 100 times more than that with a generic statin and 10 times the most expensive branded statin.[42] This would result in hardly sustainable expenses even for developed countries in case of substantial prescriptions of the new products.

In conclusion, to militate this sort of disruptive scenario for European third-party payers, we would warmly recommend the adoption of a 'price-volume'-like contract[43,44] for these products from the very beginning, in which drastic price reduction should be envisaged in case of prescriptions exceeding the appropriate therapeutic targets estimated *ex ante*.

Subsequently, systematic control of prescription patterns will be the only means of enhancing rational consumption in clinical practice, although its effectiveness is expected to vary a lot in different countries, depending on the type and management of healthcare systems, and on medical deontology too.

Declarations

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Note

a. We used 'simvastatin' OR 'lovastatin' OR 'pravastatin' OR 'fluvastatin' OR 'atorvastatin' OR 'cerivastatin' OR 'rosuvastatin' OR 'pitavastatin' AND 'cost' and 'cost analysis' as search terms. We immediately discarded 138 studies, being clinical studies (52), clinical reviews (14), meta-analyses (3), economic reviews (5), health policy studies (18), editorials (13), comments and letters

(14), surveys (4) and other topics (15). Of the 60 studies identified, we also excluded nine partial economic evaluations and 32 full economic evaluations not conducted in European settings.

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