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Preamble

Atherothrombosis, characterized by atherosclerotic lesion disruption with superimposed thrombus formation, is the primary cause of cardiovascular death, the leading cause of mortality world-wide.[1] The burden of atherosclerotic cardiovascular disease (ASCVD) is not, however, confined to mortality. With ageing populations, morbidity and disability associated with cardiovascular complications become increasingly relevant. Heart failure, the endpoint of a variety of cardiovascular disease trajectories, most notably ischaemic heart disease in developed regions[2], atrial fibrillation, a complication of acute myocardial infarction (MI) in more than 10% of cases[3], and stroke are key examples, as each confers a high risk for hospital (re)admission, multiple pharmacotherapeutic approaches, and interventional procedures. Moreover, improved management in the acute MI setting means that a greater proportion of individuals are surviving and therefore are at high risk of recurrent events.[1,4] All of these scenarios reinforce the premise that ASCVD is not just a health issue, but a major economic burden to society, with the global cost estimated to exceed one trillion US dollars by 2030.[5] Increasingly, this burden will be met by middle-income countries as their economies and populations grow and age.

Renewed efforts are needed to address the burden of ASCVD. Inherent to such efforts is a move to personalized management approaches that allow clinicians to target treatments to patients at highest risk. An urgent priority is to adapt public health approaches to risk estimation in order to reflect changing patient demographics. One solution may be incorporation of the SMART (Second manifestations of arterial disease) score, which enables clinicians to differentiate the risk of recurrent events in individuals with clinical ASCVD.[6] This approach may facilitate precise targeting of innovative therapies to individuals at highest risk, in whom the benefits are likely to be commensurate with the cost.

The aim of this critical appraisal is to throw down the gauntlet to both health economists and to clinicians involved in the management of ASCVD patients in order to clearly identify the current challenges that are faced at the crossroads between the introduction of an innovative and highly efficacious lipid lowering therapy, i.e. proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibition, and the health economic dimension (such as quality-adjusted life years [QALYs] gained) intimately linked to such therapy.

Gauntlet No. 1: Clinical challenges

The challenges in ASCVD prevention are multi-tiered. From a public health perspective, promotion of cardiovascular health, specifically targeting smoking prevention/cessation, diet quality and physical inactivity, is a pre-requisite and cost-effective base component of any programme aimed at maintaining low cardiovascular risk. Such approaches are feasible to implement on a population-basis, require only a fraction (<5%) of total health spending even in low-income countries, and confer important societal benefits, not just in terms of cost savings for healthcare systems but also for loss of productivity associated with ASCVD disability and death.[5,7] It is, however, evident that maintenance of low cardiovascular risk does not eliminate the development of preclinical ASCVD[8], highlighting the need to target intervention with non-pharmacological approaches as early as possible, ideally to children or adolescents.

In both primary and secondary prevention settings, lowering low-density lipoprotein-cholesterol (LDL-C), a major modifiable cardiovascular risk factor, must be a central part of any programme for adults. This overarching principle is supported both by evidence for the cumulative arterial burden of LDL, and by genetic data for the beneficial impact of lifelong exposure to lower LDL-C levels on lifetime cardiovascular risk.[9,10] One of the major challenges in the primary prevention setting is to identify and treat individuals at the highest risk, including

those with familial hypercholesterolaemia (FH) before the onset of clinical complications, and non-FH individuals with pre-clinical atherosclerosis. Indeed, detection of subclinical carotid or coronary atherosclerosis with non-invasive imaging may be one cost-effective strategy to improve targeting of therapeutic intervention appropriately, with the potential for gains in healthy life years.[12] Yet is clear that clinical reality lags far behind what is required.[11] For individuals with clinical ASCVD, the major challenge is to reduce the risk of recurrent events and the associated burden of hospitalization, revascularization and intensive clinical management.

For both primary and secondary prevention, statins are established first-line therapy for preventing cardiovascular events and are cost-effective in individuals with clinical ASCVD;[13,14] the addition of ezetimibe provides further benefit.[15] Yet even on optimally tolerated statin therapy, with or without ezetimibe, a proportion of high-risk patients fail to attain guideline-recommended LDL-C goal, in part due to lack of adherence, inter-individual variability in treatment response, and/or inability to tolerate statin therapy, in large part due to muscle symptoms.[16-18] These individuals have unmet clinical needs, requiring additional potent therapeutic options to attain LDL-C goal and thus reduce the risk of recurrent cardiovascular events.

There is now evidence from randomized controlled trials (RCTs) that new treatments such as PCSK9 inhibitors -which lower LDL-C levels on top of intensive statin therapy in patients with clinical ASCVD- can regress atherosclerosis as exemplified by the GLAGOV trial,[19] and equally improve clinical outcomes and survival significantly, with no evidence to suggest a LDL-C threshold for clinical benefit.[20-23] Moreover, the absolute benefit was greater in subjects at higher risk, i.e. with multivessel disease including peripheral arterial disease,[24] or

with recent or recurrent MI.[25] These findings offer the prospect of attainment of guideline-recommended LDL-C goal in all secondary prevention patients. Furthermore, significant improvement in all-cause mortality in acute coronary syndrome patients over a median follow-up of 2.8 years as recently reported in ODYSSEY OUTCOMES,[23] is highly relevant to the long-term trajectory of chronic ASCVD disease in these very high-risk patients. As these highly effective injectable treatments are administered every 2 weeks or monthly, advantages for patient adherence and convenience appear evident.

It is well recognized, however, that there is often disparity between patients in a RCT and those seen in routine care, with the latter typified by a higher prevalence of polyvascular disease and comorbidities. Evidence-based recommendations support the use of innovative therapies such as PCSK9 inhibitors in these patients.[26] The key question then is how to translate these therapies to measures of societal benefit, taking account of the timing and long-term impact of these efficacious treatments on the trajectory of ASCVD.

These uncertainties, of which cost effectiveness is a key component, have prompted the publication of a slew of analyses with varying conclusions. Some have indicated that the incremental cost of adding a PCSK9 inhibitor is prohibitive without significant discounting,[27-29] whereas others claimed that incorporation of PCSK9 inhibitor treatment in patients with clinical ASCVD or with heterozygous FH, would be below the benchmark or willingness to pay threshold for a QALY gained (typically $50,000/year).[30,31] These contrasting findings may be due to a number of factors, including the setting (US or a single country in Europe), drug costs, patient characteristics (clinical setting, baseline age, background therapy, and baseline LDL-C levels), the estimated LDL-C and event reductions (either modelled, or based on registry or trial data), the extent to which indirect costs (which are related to productivity losses due to

cardiovascular events) were incorporated, and the time horizon and perspective of the health economic analysis.

Clinicians are clearly confused by the different approaches used in these analyses. Is it possible to simplify the health economics modelling in order to anticipate the projected impact of these innovative treatments on CVD trajectory over a decade or more?

Gauntlet No. 2: Health economic challenges

Health economic models have been used for decades to evaluate the potential economic benefit of innovative agents. Not surprisingly, these models have also been applied in assessment of the value of PCSK9 inhibitors. The prevailing perception among clinicians, however, is that the final cost per QALY seems to have 'fallen from the sky'. In large part this is due to the lack of 1) clear information on the parameters considered essential for integration into modelling scenarios, and 2) the necessary support to explain the results of these assessments. Furthermore, large differences in the results reported for different studies do not generate confidence. Many, many questions emerge when clinicians try to understand and interpret these models, as highlighted below.

- *Is the considered target population a real-life population or clinical trial population?* Clinical trial populations tend to be more homogeneous than those seen in routine practice due to screening procedures that tend to exclude patients with multiple morbidities, who are likely to be more susceptible to adverse effects. Thus, the trial population may not reflect the clinical reality as shown by event rates that are usually lower than those seen in practice. Sometimes, however, the opposite is true if the clinical trial requires a minimal risk level for patient inclusion.

- *Which clinical trial data have been used to express the benefits of a new treatment?* Are treatment effects assumed beyond the duration of the trial, and if so, is there the same relative risk reduction, a waning effect or something else?
- *How long is the prediction period and does this make clinical sense?* Many models use a lifetime horizon which is often perceived by clinicians as beyond a realistic scope ("who are you to predict what's going to happen over the next 30-40 years?").
- *How many events are predicted in the scenario without and with the innovation?* Clinicians prefer to see the predicted clinical benefit of the models, not just a cost per QALY. For instance, over a period of 5 years, how many myocardial infarctions are predicted in the scenario without the new medicine and how many in the scenario with the new medicine?
- *What are the assumed consequences of the events and which management patterns have been applied?* For example, if the patient suffers a stroke, what is the probability that this is disabling and how does this correspond to the clinical reality? How many patients are in permanent residential care following that stroke? What is the assumed follow up care?
- *Which disease and treatment trajectories have been assumed?* Will avoiding a MI lead to less heart failure in the future? And if so, will only heart failure of ischaemic origin be affected, or is there an impact on all types of heart failures (including valvular)?
- *Are composite end points in clinical trials concealing benefit –or lack thereof - on specific events that are included in that endpoint? Should the composite endpoint strategy be revised in this context?*
- *Finally, and pertinent in the case of the PCSK9 inhibitors, what is the assumed impact on mortality when the duration of the clinical trial is too short or insufficiently powered to*

show a statistically significant effect? Will avoiding strokes lead to reduced cardiovascular mortality? What are the patterns of fatal events and mortality overall over time? In this context, even though the two completed trials with PCSK9 inhibitors were of relatively short duration (<3 years), an all-cause mortality benefit was observed in acute coronary syndrome patients.[23]

As long as health economists fail to clearly answer these questions, clinicians will be tempted to ignore the reported findings and, as a consequence, not adapt their practice.

A new health economics scenario for the 21st century: for and with clinicians

In order to be relevant to clinicians, health economic models should comply with several requirements (see **Box 1**). Briefly, the model should be clinically validated, transparent, use real world data to provide event rates in the target population and RCT data to provide the relative reduction in risk of these events with any new therapy, and should also consider the clinical realities of the condition and its consequences. Moreover, if the real world population has different characteristics compared to the clinical trial population (older, more comorbidities, higher LDL-C,…) and the relative risk reduction has been shown to be influenced by some of these characteristics, then the relative risk needs to be adjusted. Also, if data on clinically relevant endpoints such as MIs and strokes are lacking, then the assumed relationship between the intermediate endpoint (in this case, LDL-C reduction) and the endpoints (cardiovascular events) should be documented and justified.

Health economic models should also avoid the pitfalls of overclaiming or underclaiming benefits. An example of the former is assumption that effects from LDL-C reduction impact directly the incidence of heart failure despite the lack of evidence for any such relationship. In

contrast, underestimating the impact of stroke on quality of life has consequences, as for example, on the calculation of the incremental cost-effectiveness ratio (ICER) in US analyses when stroke was assumed to decrease quality of life by only 3%.[28]

A key question is how best to relate the impact of innovative treatments on the trajectory of ASCVD. In middle-aged individuals with a first MI, attainment of very low LDL-C levels with early initiation of a PCSK9 inhibitor on the background of statin or statin plus ezetimibe treatments has the potential for large gains in life expectancy and QALYs. Models should clarify what the health benefits are for those patients for whom more aggressive treatment really makes a difference. In those patients where MIs and strokes are prevented, what will be the impact on their lives? These benefits for the patient will undoubtedly translate to societal benefits arising from reduced morbidity and loss of productivity associated with cardiovascular complications. If, however, the requirements for access to such new treatments are restrictive, then such a promising scenario is unlikely.[32] Indeed, some have suggested that despite their established clinical value, perceived costs and budgetary concerns relating to the use of PCSK9 inhibitors in the target patient groups have led to lower than expected uptake of these treatments.[33] This is a simplistic approach, however, which does not integrate possible rebates and discounts that may be offered by the manufacturers; indeed, recent developments suggest that the budget impact of such treatments is lower than anticipated,[34] especially when weighed against the burden of cardiovascular complications.

Importantly, the outcomes of the model should be clearly reported and validated, using graphs that reflect the predicted number of clinical events over time in the model, both for the control arm (in this case, background statin or statin plus ezetimibe therapy) and the intervention arm (add-on PCSK9 inhibitor). The extent to which the model prediction for the control arm

corresponds to the observed event rate in real world datasets should be assessed. If the model underestimates the event rates in the control arm (either single or composite events), then the absolute benefit of the better therapy will be smaller, which will in turn result in a worse cost-effectiveness estimate, whereas if baseline event rates are overestimated, then this will result in more refined cost-effectiveness estimates. In either case, the model cannot be considered as validated.

A recommended approach is cross-validation. If the results of model X widely deviate from model Y, the input parameters in X can be modified sequentially to reflect those in Y. The extent to which the results of X evolve towards the results of Y for each modified parameter provides insights into the key drivers of the deviation in results. The onus is on health economists to clarify this, instead of making unconditional claims about the level of cost-effectiveness of medicines.

Take home lessons

With increasingly finite resources, the use of innovative therapies needs to be balanced against their cost relative to the substantial burden of associated cardiovascular sequelae. Health economic modelling needs to adapt to the evolving characteristics of patients, in particular taking account of the impact of new therapies, as well as the timing of initiation of such treatments, on the trajectory of ASCVD (**Summary Figure**). By following these proposed recommendations, health economic models can become informative rather than create confusion. To achieve this, it is imperative that all stakeholders in the healthcare pathway are involved in the production and interpretation of health economic models to ensure appropriate patient access to innovative therapies for prevention of cardiovascular events.

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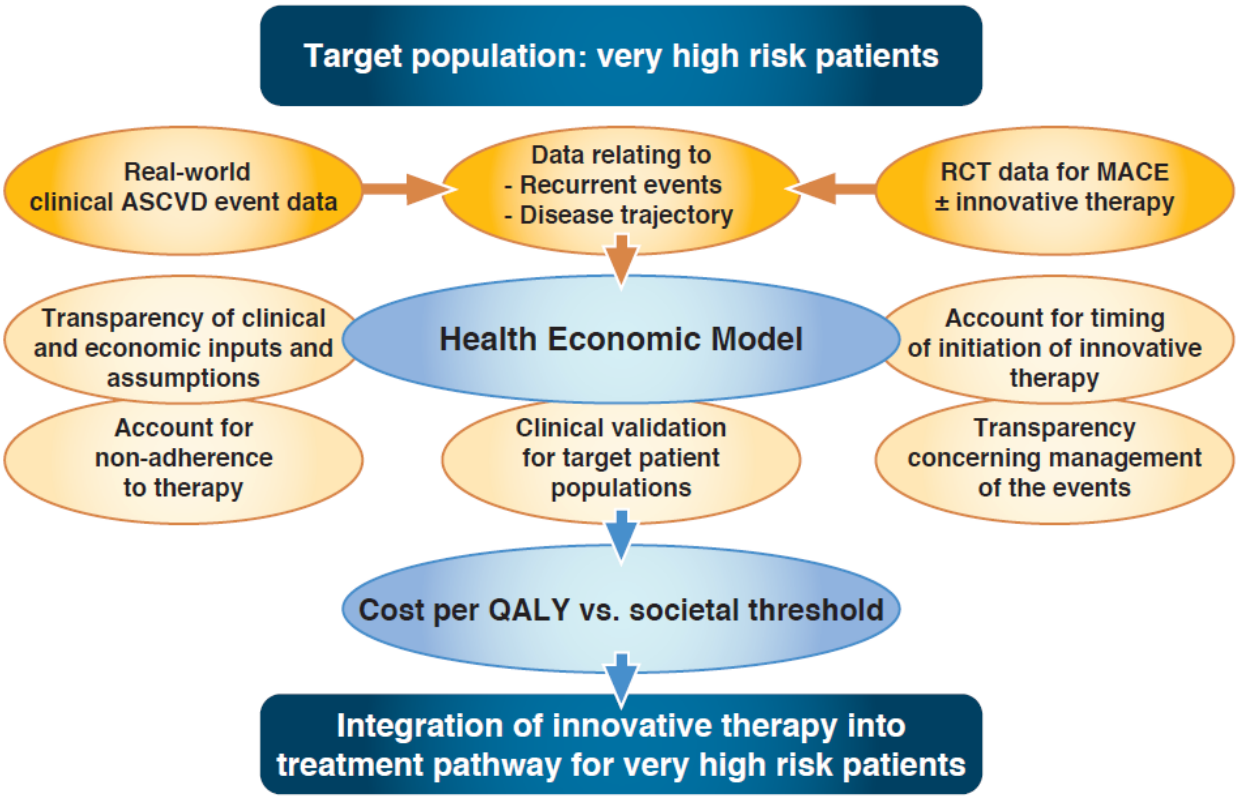
Summary Figure

Essential components of a health economic model for assessment of the cost-effectiveness of an innovative therapy for prevention of cardiovascular events in very high-risk patients.

Abbreviations: ASCVD atherosclerotic cardiovascular disease; MACE major adverse cardiovascular events; QALY quality adjusted life year; RCT randomized controlled trial



Box 1. Essential requirements of health economic models

- Clinically validated structure which correctly reflects the (combination of) clinical outcomes in the target population
- Transparency, with disclosure and justification of clinical and economic inputs and assumptions
- Derived from real world and randomized controlled trial data
- Use of age-adjusted event rates, with explanation of the adjustment
- Reflect the clinical reality in terms of event and treatment sequences
- Account for non-adherence