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Impact of Different CV Risk Estimation Methods on Cost-Effectiveness Analysis

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KEY FINDINGS & CONCLUSIONS

- In a UK ASCVD cohort, SMART risk estimates were consistently higher than CTT LDL-C–linked estimates for comparable patient profiles, indicating that LDL-centric CTT meta-analysis approaches may understate CV risk.
- The cost-effectiveness results with base case and scenario analysis with low and high-risk profile resulted in lower ICER values with SMART risk compared with CTT meta-analysis approach. These indicate that CTT meta-analysis approach is a conservative methodology and using risk estimates based on SMART risk calculator could improve ICER.

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INTRODUCTION

- Cardiovascular risk (CV risk) refers to the probability that an individual will experience a cardiovascular event (such as myocardial infarction, stroke, or CV death) over a specified period (e.g., 10 years).[1]
- The CV risk is especially pertinent for patients with atherosclerotic cardiovascular disease (ASCVD) or in patients with multiple risk factors, who face elevated CV risk. These populations are often the focus of prevention efforts and lipid lowering therapies such as statins and PCSK9 inhibitors.[1]
- Cost-effectiveness analysis (CEA) is an economic evaluation method that compares the costs and health outcomes of alternative interventions.[2] A cost-effectiveness model uses clinical inputs – including CV event risk – to project long-term outcomes (e.g., number of CV events prevented, life expectancy) and costs for patients receiving a new intervention versus standard of care. By combining costs and effects, the model produces metrics like an incremental cost-effectiveness ratio (ICER), which HTA bodies use to judge value for money.
- In CE models developed for health technology assessments (HTAs), estimating CV event risk is crucial for projecting outcomes of CV risk-reduction therapies. Many HTA submissions for lipid-lowering therapies in ASCVD population use a risk equation derived from the Cholesterol Treatment Trialists' (CTT) meta-analysis, which links the reduction in low-density lipoprotein cholesterol (LDL-C) to proportional reductions in CV event risk.[3,4,5]
- In clinical practice, multivariable risk calculators are used by clinicians to estimate an individual's CV risk by accounting for a range of risk factors.[1] For example, the SMART[6] risk score (Second Manifestation of Arterial Disease score) is a published tool that estimates 10-year risk of recurrent vascular events in patients with established arterial disease. It incorporates patient characteristics such as age, sex, blood pressure, cholesterol levels, smoking status, diabetes, and history of cardiovascular disease, among others. Other examples include the Framingham Risk Score[7] and QRISK[8,9], which similarly use multiple inputs. These clinical risk models often stratify patients into risk categories (e.g., low, medium, high risk) for recurrent events.
- Differences in how CV risk is estimated can directly impact cost-effectiveness outcomes. If one method predicts a lower absolute risk (and hence fewer events) than another, a treatment might appear to have less absolute benefit in the economic model, potentially yielding a higher ICER (less cost-effective). Conversely, a higher predicted risk could show greater absolute benefit from an intervention, improving cost-effectiveness. Understanding these differences is crucial for decision-makers and modelers; an inaccurate risk estimation method could misjudge the economic value of the drug.
- This study addresses that gap by comparing two approaches to CV risk estimation— CTT meta-analysis-based method vs. SMART risk calculator—and examining the implications for cost-effectiveness results in comparable patient groups.

OBJECTIVE:

- To compare cardiovascular event risk estimations using the SMART risk calculator versus the LDL-C centered CTT meta-analysis approach in ASCVD population.
- To quantify how much the two risk assessment methods diverge for the same cohort of patients and to assess how these differences might influence cost-effectiveness analysis outcomes.

METHODS

Population	Patients with ASCVD receiving standard of care (statins) in the UK
Data sources	• Patient demographics and clinical risk factors were obtained from Clinical Practice Research Datalink (CPRD), a large UK primary care database, focusing on variables required for risk calculations (e.g., age, sex, systolic blood pressure, lipid levels, diabetes status, smoking status, history of cardiovascular events).[10] • Data on additional parameters such as eGFR and hs-CRP was sourced from literature[6]
Estimation	**SMART Risk Calculator** • We applied the published SMART risk equation (Model A) to the average patient profile. • The average patient profile is a weighted average of diabetic and non-diabetic patients. • The SMART model computes the 10-year risk of a recurrent event based on these factors. **CTT meta-analysis based approach** • A cost-effectiveness model used in the UK HTA submission for a therapy targeting LDL-C reduction was used to compute the 10-year event risk. The population in the model included patients with either Heterozygous familial hypercholesterolaemia (HeFH), established ASCVD or Primary prevention patients with elevated risk (PPER)[10]. • In the CE model, the baseline annual risk of CV events is linked to LDL-C level via the CTT meta-analysis equation. • The 10-year CV event risk projected by the model was used for standard of care (SoC) for ASCVD population. • The baseline event risks were weighted based on the prevalence of diabetic and non-diabetic population. • The model calculated the baseline risk of events and also considered a 3% annual increase in the non-fatal event rate to account for elevated risk with age. • Scenario analysis was conducted with low and high-risk profile patients by considering +/- 10% variation from base case profile.

Description of CTT Meta-analysis Equation

$$E_i = E_{0i} * \alpha i^{L_0 - L_1}$$

- L_0 is the baseline LDL-C level in mmol/L
- L_1 is the new LDL-C level in mmol/L
- E_{0i} is the 1-year probability for experiencing event i at the baseline LDL-C level of L_0
- E_i is the 1-year probability for experiencing event i at the LDL-C level of L_1
- α_i is the "rate ratio" (RR) per unit change in LDL-C for event

Description of SMART Risk Calculator

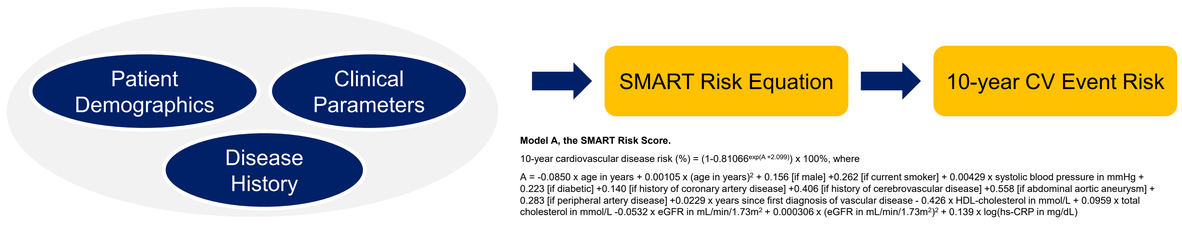
10−year event risk = f (Patient Characteristics, Clinical Parameters, Disease History)

Patient Characteristics	Clinical Parameters	Disease History
Age In Years	SBP (per 10 mmHg)	Years since 1st CV Event
Male Sex	Total Cholesterol	CVD History
Diabetes Status	HDL	CAD History
Current Smoking	hs-CRP	AAA History
	eGFR	PVD History

Patient Information used in the calculation of CV event risk

Variable	Base Case Profile	Low Risk Profile	High Risk Profile
Age In Years	68.77	61.89	75.64
Male Sex	0.55	0.49	0.60
Diabetes %	0.16	0.15	0.18
Current Smoking %	0.23	0.21	0.26
SBP (per 10 mmHg)	137.75	123.97	151.52
Total Cholesterol	4.87	4.38	5.35
HDL	1.39	1.25	1.53
hs-CRP	2.20	1.98	2.42
eGFR	76.00	83.60	68.40
Years since 1st CV Event	1.86	1.68	2.05
CVD History	0.19	0.17	0.21
CAD History	0.91	0.82	1.00
Abdominal aortic aneurysm (AAA) History	0.00	0.00	0.00
PAD History	0.09	0.08	0.10
LDL	3.47	3.13	3.82

Calculation of CV event risk based on SMART risk Calculator

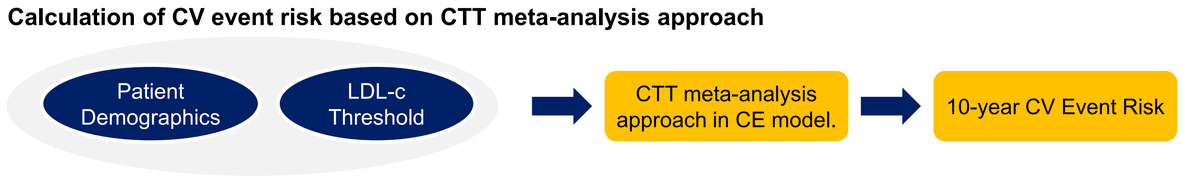


Model A, the SMART Risk Score.

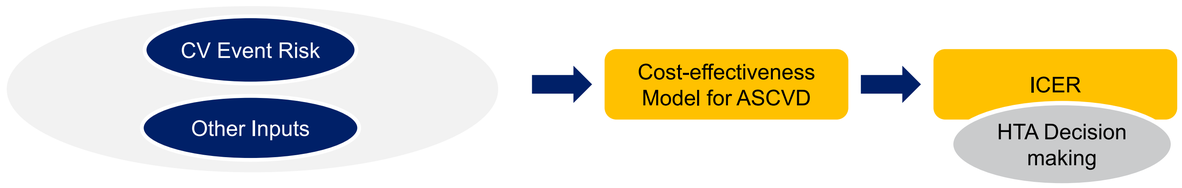
10-year cardiovascular disease risk (%) = $(1-0.81066^{\exp(A+2.099)}) \times 100\%$, where

A = -0.0850 x age in years + 0.00105 x (age in years)^2 + 0.156 [if male] +0.262 [if current smoker] + 0.00429 x systolic blood pressure in mmHg + 0.223 [if diabetic] +0.140 [if history of coronary artery disease] +0.406 [if history of cerebrovascular disease] +0.558 [if abdominal aortic aneurysm] + 0.283 [if peripheral artery disease] +0.0229 x years since first diagnosis of vascular disease - 0.426 x HDL-cholesterol in mmol/L + 0.0959 x total cholesterol in mmol/L -0.0532 x eGFR in mL/min/1.73m^2 + 0.000306 x (eGFR in mL/min/1.73m^2)^3 + 0.139 x log(hs-CRP in mg/dL)

Calculation of CV event risk based on CTT meta-analysis approach



Use of CV event risk in Health economic model

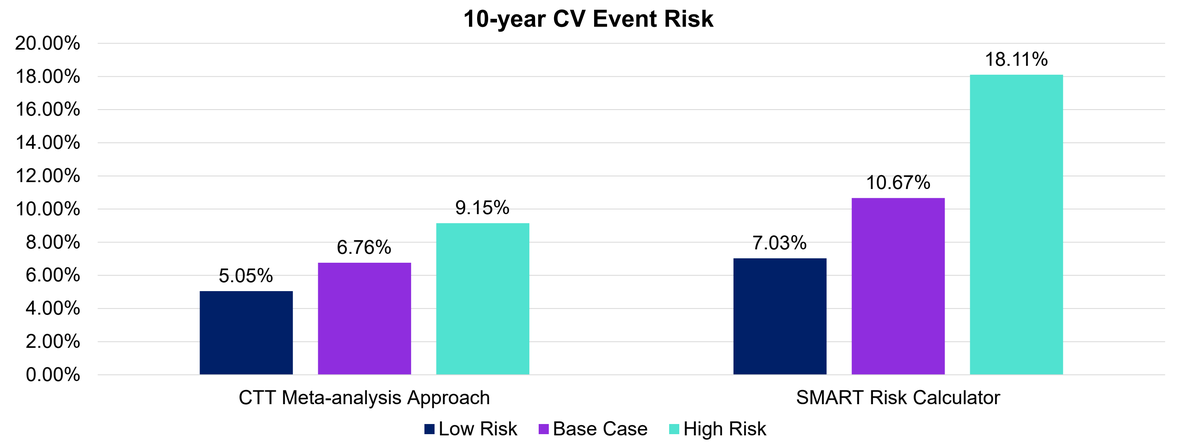


ASCVD, atherosclerotic cardiovascular disease; CV, cardiovascular; HTA, health technology assessment; ICER, incremental cost-effectiveness ratio

RESULTS

- For the base case cohort (mean age ~68 years; 55% male; 16% diabetic), the SMART calculator estimated approximately a 10.67% risk of a CV event within 10 years for a patient on standard therapy (statins). In contrast, the CTT-based approach estimated about 6.76% 10-year risk for the same average profile.
- In scenario analysis, a low risk and high-risk profile of patients was considered. For low-risk patients, the estimated 10-year risk was 5.05% based on the CTT meta-analysis approach and 7.03% based on the SMART risk calculator. For high-risk patients, the estimated 10-year risk was 7.03% based on the CTT meta-analysis approach and 18.11% based on the SMART risk calculator.

10-year CV Event Risk



Discussion

The CTT meta-analysis approach (commonly used in HTA models) produced lower 10-year CV risk estimates compared to the SMART risk calculator for the same cohort. In the analysis, using only CTT meta-analysis approach led to an underestimation of absolute risk, as it may not fully capture all individual risk factors.

The scenario analysis with low and high-risk profile reflected similar results with CTT meta-analysis approach underestimating the 10-year risk compared with the SMART calculator estimates.

Importantly, using SMART risk estimates in a cost-effectiveness model for LDL-lowering therapy produced lower ICERs than the CTT meta-analysis method. Specifically, the ICER derived from the SMART risk calculator was 28% lower compared to the ICER based on the CTT meta-analysis approach. This suggests that published ICER estimates for LDL-lowering therapies may be higher and therefore conservative. Since most of the published cost-effectiveness estimates for lipid lowering therapies use CTT meta-analysis approach, results generated using SMART risk approach would only improve the cost-effectiveness results.

It is important for health economists and modelers to choose a risk estimation approach that is appropriate to the context. Therefore, this study underscores the need for further research into validating and calibrating risk estimation methods in diverse real-world populations.

Additionally, exploring hybrid approaches in the economic models (e.g., using multivariable risk scores but calibrating them to trial-based risk reductions) might combine the strengths of both methods.

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