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Original Article

Estimating the cost-effectiveness of screening a general population for cardiovascular risk with high-sensitivity troponin-I

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Aims To estimate the cost-effectiveness of using the cardiac specific marker high-sensitivity troponin-I (hsTnI) for assessing cardiovascular disease (CVD) risk in a general population.

Methods and results A discrete-event simulation model was developed from a societal perspective of a low-risk (Germany) and a high-risk (Kazakhstan) country. The model compared a Screen&Prevent strategy guided by hsTnI against a do-nothing strategy. Risk functions were derived from published data of a prospective cohort study [Nord-Trøndelag Health (HUNT) Study]. The model assessed the number of CVD events and deaths, healthy life years, direct and indirect costs in PPP 2018 Dollar, and quality-adjusted life years (QALY) over a time horizon of 10 years. Screen&Prevent reduced the number of CVD events per 1000 subjects by 5.1 and 5.0, equal to a number-needed-to-screen of 195 and 191 in Kazakhstan and Germany. Screen&Prevent was cost saving in Kazakhstan and cost-effective in Germany with an incremental-cost-effectiveness ratio of $6755 ($2294; $24 054) per QALY gained at an opportunity-cost based willingness-to-pay threshold of $27 373. Varying input variables in univariate and probabilistic sensitivity analyses confirmed the robustness of the analysis.

Conclusion Assessing the cardiovascular risk with hsTnI in a general population and subsequently referring those at high risk to preventive means would very likely be cost-effective or cost-saving by avoiding CVD events and associated direct and indirect costs. This conclusion is retained even if only the direct costs or only the costs for screening and prevention are considered. Future studies should evaluate the incremental cost-effectiveness of hsTnI-guided assessment strategies against established risk algorithms.

Keywords High-sensitivity troponin-I • Biomarker • Risk assessment • Cardiovascular disease • Cost-effectiveness

Introduction

Cardiovascular disease (CVD) is the single largest contributor to the worldwide health burden and the number one cause of death globally.[1] The total economic burden of CVD in the European Union was estimated to €210 billion in 2015 with 53% and 21% accounted for by direct medical costs and productivity losses.[2] To decrease the burden of CVD, reliable tools are required to identify persons without known CVD who are at risk and to guide those persons to lifestyle modifications or preventive medication.[3,4] Several screening or risk assessment strategies have been recommended and are partly established.[4] Most of which are based on various risk algorithms, such as the Framingham Risk Score, Q-Risk, or the SCORE (Systematic Coronary Risk Evaluation) risk calculator, that were derived from large cohort studies.[3,5–7] A cardiac specific biomarker high-sensitivity troponin-I (hsTnI) has been found detectable in 96% of the general population.[8,9] In addition, it has been shown that elevated hsTnI values can not only be associated with incident fatal and non-fatal CV

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events but also lead to an increased net reclassification improvement.[10,11] Since hsTnI provides independent prognostic information for future CVD,[12] the use of the marker for targeted prevention has been suggested.[10,12] Still, the size of downstream effects of using hsTnI in primary prevention has not been evaluated so far. In addition, a recent survey has indicated that the lack of information on cost-effectiveness is one of the main barriers for the implementation of a biomarker.[4] Therefore, the objective of our study is to get an early estimation of potential health economic benefits and cost-effectiveness of using hsTnI for assessing cardiovascular disease risk in an asymptomatic population.

Methods

Principal model design

A discrete-event microsimulation (DES) model was developed from a societal perspective of a low-risk (Germany) and a high-risk country for CVD (Kazakhstan). This model type was chosen to apply hazard risk functions derived from a large prospective trial to simulate individual and competing event times. The model compared two strategies in terms of the incidence of cardiovascular events over ten years. For the purpose of this early estimation, we did not consider a guideline recommended risk stratification as the standard strategy. Instead, the standard refers to a do-nothing strategy (no risk stratification, no prevention). In the alternate strategy (Screen&Prevent), individuals were screened with hsTnI and assigned to risk categories for CVD by applying gender specific diagnostic cut-offs [low risk: hsTnI <4 ng/L for women, < 6 ng/mL for men; moderate risk: 4–10 ng/L (women), 6–12 ng/L (men); high risk: >10 ng/L (women), >12 ng/L (men)].[12] Subjects in the highest risk category received preventive medication. All individuals entered the model in an asymptomatic condition. The model simulated whether a CVD event occurred during the follow-up time. In case of a non-fatal event, individuals moved into a post-CVD state until they died either from CVD or any other causes, or they exited the model after the end of the time horizon. The principal model structure is illustrated in Fig. 1, input assumptions are summarized in *Table 1*.

Population, risk functions, and time-to-event

The model was informed by a study reporting on the largest prospective population-based cohort study [the Nord-Trøndelag Health (HUNT) Study] of subjects in Norway.[12] This study enrolled 9005 participants without previously known CVD from the county of Nord-Trøndelag as a second wave of the HUNT cohort (HUNT2) and were carried out from August 1995 to June 1997. In the study, the biomarker hsTnI was measured with the Abbott Diagnostics Architect STAT High Sensitive Troponin-I assay.[12] For the purpose of our study, cohort information was reconstructed from published Kaplan–Meier curves and the number of subjects at risk according to hsTnI risk categories.[12] It should be noted that in the underlying study, a classification by any other risk assessment algorithm was not available. A copy of the figure was imported into a digitization programme.[28] At several time points for each of the cohorts, the coordinates of survival probabilities were extracted. This information and the stated number of persons at risk were used to estimate the number of events and censorships in three-monthly intervals as suggested by Hoyle and Henley.[29] Censorship was assumed to be constant over the respective time interval. Afterwards, parametric models were fitted to the reconstructed data by the method of maximum likelihood and assuming a Weibull distribution. We did not assume proportional-hazards between risk categories, therefore, equations for each category were estimated separately. The time to CVD event (TTE) were sampled per each individual by risk category from the respective Weibull distributions. If the sampled TTE was shorter than the time horizon, a CVD event occurred. For persons assigned to preventive medication, a hazard ratio (HR) for statin treatment was applied to the risk function.[16] Weibull distribution parameters were adjusted to the HR by the following formula: $HR = (b_0/b_T)^{\alpha}$, where b_0 and b_T denote the Weibull scale parameter for the untreated and treated arm, respectively, and α represents the Weibull shape parameter. Cardiovascular disease-related mortality after an acute event was retrieved from a Dutch study by assuming a constant incidence rate.[14] Since individuals who died from non-CVD causes were censored in the underlying cohort, the model did not account for additional background mortality for individuals in the asymptomatic state. Background mortality in the post-CVD state were estimated from country-specific life tables by considering the age at CVD event.[15] The model assumed a population that remains in working age (<65 years) until end of the analysis.

Costs, utilities, and outcomes

Effectiveness of strategies was measured in terms of CVD events, CVD deaths, healthy life years (HLY), and quality-adjusted life years (QALY). According to the underlying study, CVD referred to a composite endpoint of hospitalization for acute myocardial infarction or heart failure, or cardiovascular death.[12] The evaluation followed a societal perspective. Direct medical costs comprised expenditures for screening, preventive medication, and costs for CVD hospitalization. For Kazakhstan, screening costs were taken from 2018 tariffs for troponin testing (Code B06.488.006) and physician visits (Code A01.001.000).[17] Costs for CVD hospitalization were estimated from 2018 tariffs for ICD I21.0–I22.9 (DRG 102).[17] For Germany, screening costs were obtained from the German Scale of Medical fees considering blood sampling, troponin testing, and consultation with increased expense factor (GOÄ 150, 250, 4069).[18] Hospitalization costs were estimated from a case mix of Diagnosis Related Groups weighted for ICD I21.0–I21.9 and multiplied with an average 2018 base rate of €3467.30.[19,20] Annual costs for statin medication were derived from a German cost analysis.[22] For Kazakhstan, costs of preventive medication were taken from an official price list assuming a daily dosage of 20 mg atorvastatin.[21] Direct medicals costs were not considered for subjects in a post-CVD state. Also, direct costs were not varied between individuals assuming average mean costs as derived from reimbursement codes.

Indirect costs were assessed from CVD-related productivity losses in the working population. Losses took workplace absenteeism, presenteeism, reduced employment, and lost productivity due to premature death into account. The gross domestic product (GDP) per employed person was calculated from country specific GDP by considering the total labour force and subtracting those who were unemployed.[13] The number of fatal events before the retirement age were adjusted with the labour force participation and unemployment rate. To calculate the loss in productivity associated with premature death, this product was multiplied with the GPD per employed person assuming a friction period of one year to replace the worker. The proportion of employees who did not return to work after a CVD event were assessed from a Dutch survey following employed patients.[23] Productivity costs associated with premature death or reduced employment assumed a friction period of one year. The reductions in productivity due to absence from work (absenteeism) and reduced work performance (presenteeism) were both derived from US studies.[24,25] To estimate productivity losses from absenteeism, and presenteeism, the reduction factors were applied to the working years after a non-fatal event to the end of the model horizon multiplied by the GDP per person employed.

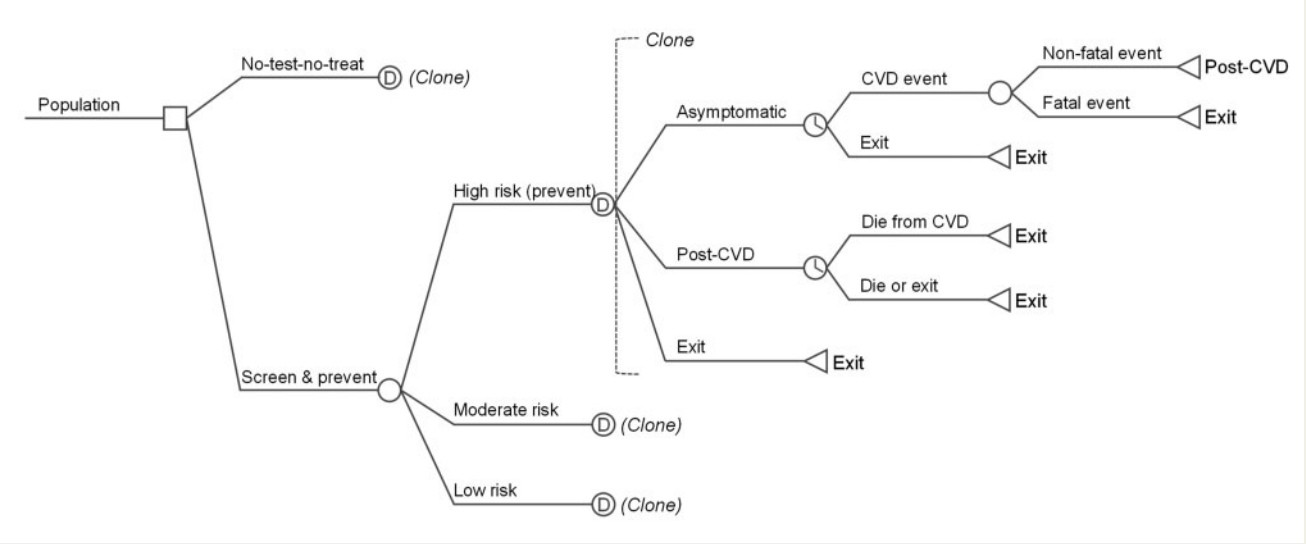

Figure 1 Model structure.

If required, all costs were first converted to the local currency using the exchange rate of the time the data were collected. Local costs were adjusted for inflation by using the GDP implicit price deflator and converted to purchasing power parity (PPP)-adjusted US$2018.[13,30] Future costs and benefits were discounted into a present value with a fixed discount rate of 3%. Cost-effectiveness was discussed based on the lowest willingness-to-pay (WTP) thresholds for highly cost-effective strategies suggested by the World Health Organization (one time the gross domestic product per capita. Germany: $54 457; Kazakhstan: $26 172),[31] and an opportunity-cost based estimate (Germany: $27 373; Kazakhstan: $14 529).[32]

Model calculations, sampling, and statistics

The model was developed in TreeAge Pro 2020 (TreeAge Software, Williamstown, MA, USA) and in accordance to the guidelines for good research practices in modelling and reporting provided by the International Society for Pharmacoeconomics and Outcomes Research[33] (Supplementary material online, *Table S5*). Curve fitting, parametrization, and statistical analyses were performed in Minitab Statistical Software 19 (Minitab, LLC, State College, PA, USA). The decision-analytic analysis was performed using a first-order Monte Carlo microsimulation. Individual characteristics were randomly sampled per each trial from respective distributions. The base case analysis used a sample size of 25 000 so that the pooled standard deviation of costs and QALYs of strategies in ten independent runs were lower than the mean difference. Comparisons between strategies were made based on mean outcome values. Confidence intervals in the base case analysis were derived from 25 independent repetitions of the base case analysis. Confidence intervals for incremental cost-effectiveness ratio (ICER) were estimated from the 2.5th and 97.5th percentile of the ICER distribution. Statistical significance was analysed conducting a two-sample *t*-test with a significance level of 0.05.

Model validation and sensitivity analyses

Model validation was conducted in several steps.[34] The estimated hazard functions were graphically compared to the Kaplan–Meier curves of the reconstructed cohort data and statistically validated with a Wilcoxon–log-rank test, a signed rank test, and the Mann–Whitney test. Model structure and assumptions were informed by an extensive literature review.[35] Input assumptions, data sources, formulas, and results were critically reviewed by experts. Individual trackers were used to capture individual outcomes and to validate model calculations. Model outcomes were validated by analysing the survival curves from the standard strategy and the reconstructed cohort data by using a log-rank and Wilcoxon statistical test.

Univariate sensitivity analyses were conducted on all variables by varying input values between the lower and upper bound as stated in *Table 1*. Results in terms of incremental costs, incremental QALYs, and incremental net monetary benefit (INMB) were reported as tornado diagrams. For INMB, QALYs were multiplied with the country specific opportunity-cost based WTP threshold. Then, total costs were subtracted from the product. A positive INMB indicated that the alternative was the preferred strategy. Probabilistic sensitivity analysis (PSA) was performed by applying a second-order Monte Carlo simulation of critical variables in 50 iterations of the microsimulation.

Results

The overall survival plot of the standard strategy simulated by the model showed an excellent concordance to the stratified Kaplan–Meier plots of the reconstructed data (log-rank and Wilcoxon test $P > 0.89$) (Supplementary material online, *Figure S1*). The alternate strategy (Screen&Prevent) reduced the number of CVD events per 1000 subjects by 5.1 (95% CI: 3.9–5.6) and 5.0 (95% CI: 4.6–5.6) in Kazakhstan and Germany, respectively. This reduction in CVD risk translated into a number needed to screen (NNS) to prevent one event of 195 (95% CI 185–217) and 191 (95% CI 187–215) for Kazakhstan and Germany, respectively. Screen&Prevent reduced costs in Kazakhstan (-$56; 95% CI: -$76 to -$26) and was more costly in Germany ($94; 95% CI: $60–$139). On average, Screen&Prevent gained 28 or 27 healthy life years per 1000 subjects in Kazakhstan or Germany which translates into 14.6 (Kazakhstan; 95% CI 10.5–17.0) and 13.9 (Germany; 10.2–15.1) additional QALYs. In summary, Screen&Prevent was found a cost-saving alternative by dominating

Table 1 Model variables and assumptions

Variables	Base value	Sampling	Low[a]	High[a]	Source
Time horizon	10	Fixed	5	15	
People with hsTnI W > 10, M > 12 ng/mL (HighT), %	4.6	Beta/dirichlet	2.0	10.0	12
People with hsTnI between 4–10 (F) or 6–12 ng/mL (M) (ModT), %	18.4	Beta/dirichlet			12
People with hsTnI < 4 (F), <6 (M) (LowT), %	77.0	Beta/dirichlet			12
Medium age at baseline	55	Fixed	45	65	
Gross Domestic product per capita (KAZ), PPP 2018$	26 172	Fixed	-10%	+10%	13
Gross Domestic product per capita (GER), PPP 2018$	54 457	Fixed	-10%	+10%	13
Labor force participation (KAZ), %	76.5	Fixed	70	100	13
Labor force participation (GER), %	78.5	Fixed	70	100	13
Unemployment rate (KAZ), %	4.9	Fixed	-10%	+10%	13
Unemployment rate (GER), %	3.8	Fixed	-10%	+10%	13
Retirement age	65	Fixed			
CVD deaths among people who reached the composite endpoint, %	45.2	Beta	40.0	50.0	12
Time to CVD event: Hazard function (LowT), Weibull shape	1.235	Weibull	1.103	1.383	Derived from[12]
Time to CVD event: Hazard function (ModT), Weibull shape	1.158	Weibull	1.033	1.298	Derived from[12]
Time to CVD event: Hazard function (HighT), Weibull shape	0.954	Weibull	0.816	1.114	Derived from[12]
Time to CVD event: Hazard function (LowT), Weibull scale	179.30	Weibull	132.51	242.60	Derived from[12]
Time to CVD event: Hazard function (ModT), Weibull scale	58.97	Weibull	48.31	72.00	Derived from[12]
Time to CVD event: Hazard function (HighT), Weibull scale	32.86	Weibull	25.91	41.67	Derived from[12]
Annual Post-CVD mortality, %	5.8	Beta	5.5	7.7	14
Non-CVD related death	Country specific lifetables				15
Hazard ratio of preventive medication	0.56	Beta	0.49	0.69	16
Screening costs (KAZ), PPP 2018$	23.99	Fixed	-25%	+25%	17
Screening costs (GER), PPP 2018$	89.31	Fixed	-25%	+25%	18
Hospitalization costs for CVD event (KAZ), PPP 2018$	1812	Fixed	-25%	+25%	17
Hospitalization costs for CVD event (GER), PPP 2018$	6588	Fixed	-25%	+25%	19,20
Annual costs for medical prevention (KAZ), PPP 2018$	128.70	Fixed	-25%	+25%	21
Annual costs for medical prevention (GER), PPP 2018$	741.32	Fixed	-25%	+25%	22
Annual discount rate for costs, %	3.0	Fixed	0.0	5.0	
Proportion not returned to work, %	12.0	Fixed	9.0	15.0	23
Reduction in productivity due to absenteeism, %	1.4	Fixed	0.5	2.5	24,25
Reduction in productivity due to presenteeism, %	3.6	Fixed	2.5	4.0	25
Baseline utility weight	0.98	Beta	0.95	0.99	
Utility decrement under preventive medication	0.01 (0.05)	Beta	0.008	0.012	26
Utility for CVD event	0.67 (0.34)	Beta	0.63	0.70	27
Post-CVD utility weight	0.82 (0.17)	Beta	0.78	0.86	27
Annual discount rate for utility weights, %	3.0	Fixed	0.0	5.0	

CVD, cardiovascular disease; PPP, purchasing power parity; KAZ, Kazakhstan; GER, Germany.
[a]Boundaries used in univariate sensitivity analyses.

the standard strategy (Higher QALYs, lower costs) in Kazakhstan. In Germany, the alternate strategy was cost-effective with an ICER of $6755 per QALY (95% CI 2294 to 24 054) (*Table 2*). Results were confirmed in probabilistic sensitivity analyses (Supplementary material online, *Table S1* and *Figure S4*). Against both WTP-thresholds, the WHO threshold and the opportunity cost-based threshold, Screen&Prevent proved to be dominant or cost-effective in 100% of the probabilistic simulations. In Germany, the alternate strategy proofed to be cost-effective with at least 95% probability down to a WTP of $12 000 per QALY which is far lower than both considered WTP thresholds (Supplementary material online, *Figure S5*). The impact of variation in variable assumptions on model results was tested in univariate sensitivity analyses and is shown as tornado-diagrams in *Figure 2*, Supplementary material online, *Figures S2 and S3*. Model results were most sensitive to the effects and costs of medical prevention, the hazard functions, the proportion of people classified as high risk, the friction period, and the time horizon of the analysis. By changing input variables in univariate sensitivity analysis within intervals as shown in *Table 1*, Screen&Prevent remained the preferred strategy in both countries. For proportions of people in the high-risk category below <2%, the ICER in the context of Germany ranged between the opportunity cost-based WTP and the WHO

Table 2 Cost-effectiveness of strategies

Outcome	Mean value per strategy		Difference	
	No Screening	Screen&Prevent	Mean	95% CI
Kazakhstan				
Costs ($)	1244	1188	-56	(-76; -26)[a]
QALY[b]	8324	8338	14.6	(10.6; 17.0)[a]
CVD events[b]	55.0	49.9	-5.1	(-6.0; -4.2)[a]
CVD related deaths[b]	30.2	27.2	-3.0	(-3.6; -2.2)[a]
HLY (years)[b]	9736	9765	28	(24.0; 33.4)[a]
ICER			Dominant	
Germany				
Costs ($)	2752	2846	94	(60; 139)[a]
QALY[b]	8330	8344	13.9	(10.2; 15.1)[a]
CVD events[b]	55.8	50.6	-5.0	(-5.7; -4.6)[a]
CVD related deaths[b]	32.9	29.2	-2.9	(-3.5; -2.3)[a]
HLY (years)[b]	9733	9760	27	(25.1; 31.7)[a]
ICER			6755	(2294; 24 054)[c]

Costs in PPP 2018 I$. Dominance in Kazakhstan refers to a negative ICER caused by a situation in which the alternate strategy is both more effective and less costly. 95% CI of mean difference was estimated from 25 repetitions of the base case analysis.
CVD, cardiovascular disease; HLY, healthy life years; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-years;
[a]*P*-value < 0.001.
[b]Per 1000 subjects.
[c]95% CI estimated from the 2.5th and 97.5th percentile of the distribution of ICER values from 25 repetitions of the base case analysis.

threshold for very cost-effective strategies (Supplementary material online, *Figure S6*). The effects of prevention measures only become apparent after several years: considering the most conservative WTP, threshold values for Screen&Prevent to become the preferred and cost-effective strategy were 2.6 and 5.0 years for Kazakhstan and Germany (Supplementary material online, *Figure S7*). Changing the shape and scale parameters of the risk functions in bivariate sensitivity analysis within the estimated confidence intervals did not result in any change in preference. Testing the costs against the hazard ratio of prevention showed that the ICER exceeded the opportunity-based WTP in Germany when approaching the unfavourable 95% confidence limit of the statin effectiveness and for higher prevention costs (Supplementary material online, *Figure S8*). Testing the impact of treatment efficacy on the ICER beyond the confidence interval stated in the assumptions, revealed that Screen&Prevent is cost-effective in Germany if the HR of preventive medication is below 0.82 (Supplementary material online, *Figure S9*). A break-down of costs that accrue over time shows that investments in screening and prevention were offset by a 9% reduction in direct medical costs for treating acute events and were mainly compensated by avoiding indirect costs (Fig. 3). Varying the time required to replace a working person (friction period) between 3 months and 1.5 years did not change the preferred strategy (Supplementary material online, *Figure S6*). Fully excluding indirect costs, the alternate strategy was still cost-effective in both countries even at the more conservative WTP (ICER per QALY gained: Kazakhstan: $4149; Germany: $23 317).

Discussion

This analysis, to our knowledge, is the first to estimate the cost-effectiveness of using hsTnI for risk assessment in primary prevention of cardiovascular disease. We developed a discrete-event simulation model from a societal perspective of two countries, Germany and Kazakhstan, and compared a screen-and-prevent strategy in a population at working age with a do-nothing strategy. It is important to stress that we were using this extreme scenario just as a baseline assumption for a first estimation of the potential cost-effectiveness of hsTnI in this area. The comparison was made in terms of the occurrence of CVD events and accrued direct and indirect costs over a follow-up period of 10 years, which is consistent to the prediction horizon of most recommended assessment tools.[36] Guiding people in a general population to preventive medication based on elevated hsTnI values led to a 9% decrease in CVD risk, reduced CVD related mortality by 8.8% (Germany) or 9.8% (Kazakhstan), and gained 27 (Germany) or 28 (Kazakhstan) healthy life years before the retirement age per 1000 people. In both countries, <200 people would need to get screened in order to prevent one CVD event. In summary, the Screen&Prevent strategy was found cost-saving in Kazakhstan and cost-effective for Germany considering very conservative cost-effectiveness thresholds. Results were proven robust over a wide range of input assumptions.

Although risk assessment programmes for CVD are recommended by guidelines,[36] these tools have several inherent limitations that have been acknowledged, such as the restricted age range (not applicable in individuals below 40 and above 65 years), or that only fatal CVD events have been included in the risk estimation.[37] In addition, their general evidence is still inconclusive.[3,38–40] Most of this can

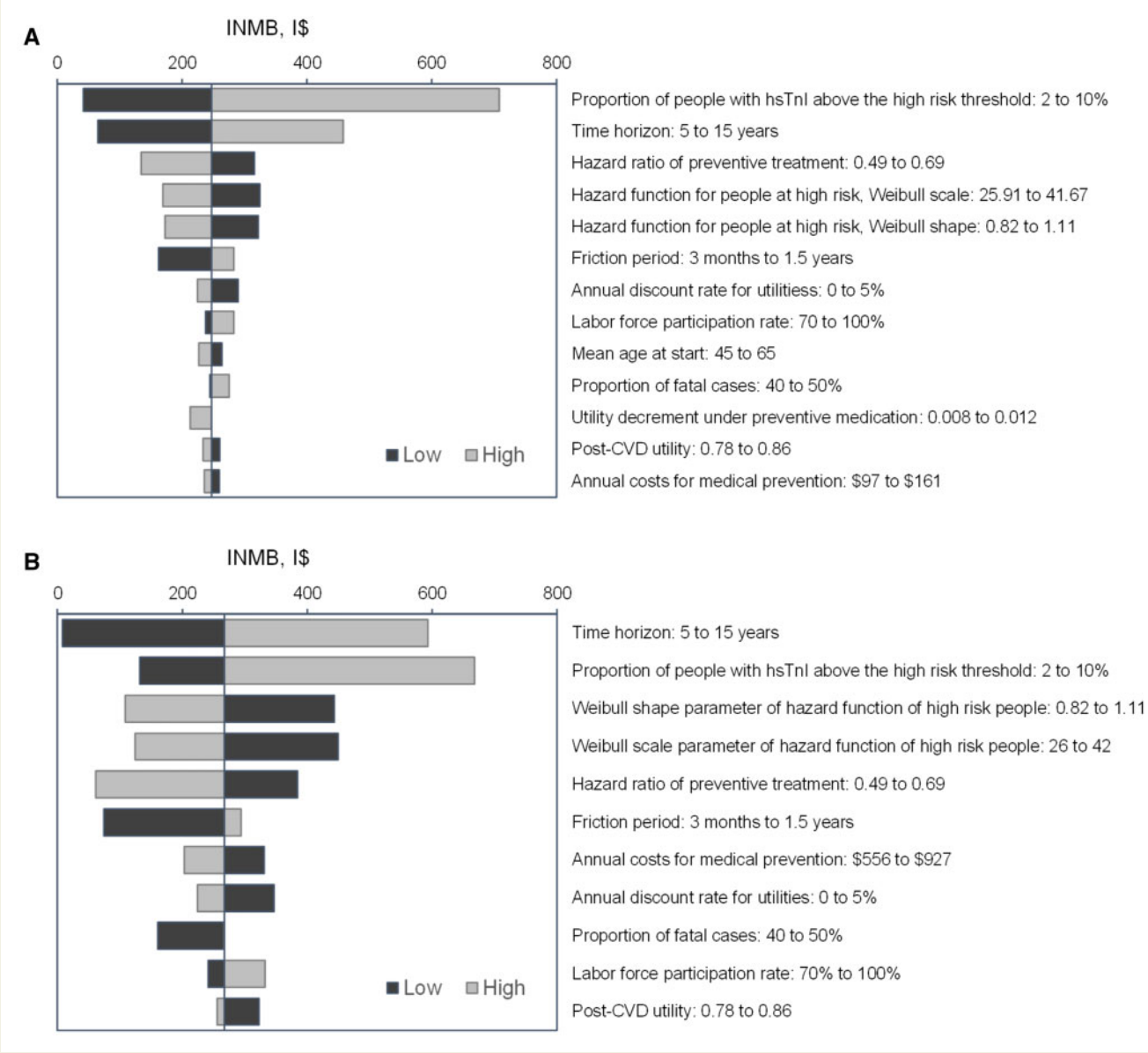

Figure 2 One-way-sensitivity analysis tornado diagrams. Kazakhstan (*A*) and Germany (*B*). INMB, Incremental net monetary benefit assuming a willingness-to-pay threshold of $14 529 (Kazakhstan) and $27 373 (Germany). A positive INMB indicates Screen&Prevent as the preferred strategy. More details are provided in the Supplementary material online.

be explained by differences in population, study design, and assessment methods. While SCORE, the risk tool endorsed by the European Society of Cardiology, is the most widely used in Europe, important variations in the implementation of risk assessment tools exists, and a survey also revealed that risk assessment tools are still not part of clinical practice in more than 20% of cases.[4] Consequently, new approaches are requested to guide primary prevention for CVD,[37] and the use of hsTnI has been discussed as a marker that is both, cardiac specific and provides independent prognostic value.[10] Still, clinical trials that directly investigate the effects of hsTnI risk assessment in primary prevention for CVD have not yet been conducted and may be hard to establish given the long follow-up times. In addition, the lack of health economic information was regarded a major barrier to the uptake of a biomarker.[4] In this phase of the evidence generation process, health economic modelling has been suggested as tool of choice.[41]

While several cost-effectiveness studies evaluated different risk assessment programmes,[42–44] a systematic review failed to aggregate information due to variations in the population, setting, study design, or modifications in the tested programmes.[45] One study evaluated a screening strategy using low LDL and elevated high-sensitivity C-reactive protein (hsCRP) followed by statin treatment for subjects regarded as high risk.[46] Compared to a no-test-no-treat strategy, this biomarker guided approach was found cost-effective in the USA (ICER in 2009 US$: $25 198 per QALY) and accumulated 310 incremental QALYs in 1000 subjects over lifetime. In our study, even if the

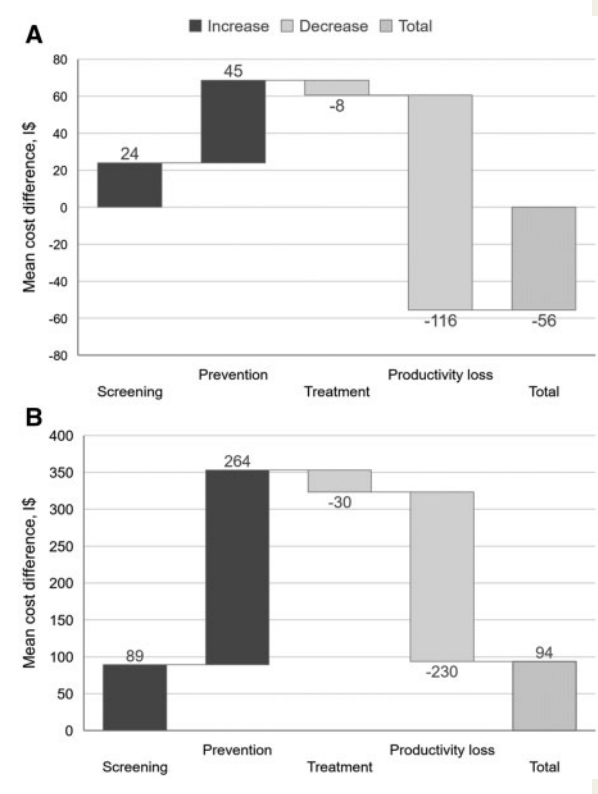

Figure 3 Incremental costs by cost type. Waterfall diagrams of the difference in costs per each cost type for Kazakhstan (*A*) and Germany (*B*). Investment in screening and prevention, savings in costs for treating CVD events, and reduced productivity losses sum up to total incremental costs of -$56 (Kazakhstan) and $94 (Germany). All costs in PPP 2018$.

time horizon was extended from 10 to 15 years, the effect did not exceed 30 QALYs per 1000 persons (Supplementary material online, *Figures S2 and S3*). However, the study that we used to derive risk functions also demonstrated that hsTnI provides a better reclassification and prediction accuracy compared to hsCRP.[12] Therefore, a hsTnI-guided strategy should generate more health economic benefits than a hsCRP one. Besides different settings and populations, a comparison of our results to the previous study indicates that our model followed more prudent assumptions and results can, therefore, be considered conservative.

This conclusion is also endorsed by the following points:

A study estimated that hospitalization costs in the acute phase accounted for only 49% of the total direct medical costs in patients with MI in the first year.[47] In our evaluation, direct medical costs took only acute hospitalization costs into account. Therefore, our study underestimated the costs accumulated over the time following an event. As shown in sensitivity analyses, although this variable does not have a substantial impact on model result, higher costs associated with an event would further improve the cost-effectiveness of the Screen&Prevent strategy (Supplementary material online, *Figure S3*).

Caused by several factors such as culture, ethnicity, economics, geography, and risk factor prevalence, the risk for CVD varies considerably between countries.[1,2] According to European guidelines, Norway and Germany are among the countries classified as low-risk for cardiovascular mortality, whereas Kazakhstan is regarded as very-high risk.[37] Risk functions used in our evaluation were derived from the HUNT-study, a Norwegian cohort enrolled between 1995 and 1997.[12] It consists data from a large prospective cohort with a long follow-up (median follow-up: 13.9 years) and a substantial number of clinical outcomes, including admissions for acute myocardial infarction, admissions for heart failure, and CV deaths.[12] While the HUNT cohort can generally provide a good resource for a simulation model, the baseline hazard as well as prevalence and incidence of cardiovascular risk have likely changed over time and cannot be adopted to Germany and Kazakhstan without caution. In the absence of country specific information, the applicability of the derived risk functions to other countries may be best assessed by comparing the event incidence rate. Over the study period in Norway between 1995 and 2004, the incidence of IHD, which is the most common manifestation of CVD, decreased from 197 to 166 per 100 000 population.[2] In 2017, the IHD incidence in Kazakhstan and Germany was estimated to be 217 and 172 per 100 000, respectively.[2] Therefore, the Norwegian cohort should reflect the risk in Germany relatively well, but underestimate the risk in Kazakhstan. Assuming that the proportion of subjects classified as high risk is correlated to the incidence, sensitivity analyses suggest that the ICER remains relatively stable with increasing proportion of people at high risk (Supplementary material online, *Figure S6*). Therefore, the relative cost-effectiveness and preference for the Screen&Prevent strategy should not change even if the assumed risk is lower than the observed risk, as is the case in Kazakhstan.

Given that CVD is one of the leading causes of mortality under 70 years, premature deaths are of specific interest and in the focus of prevention programmes.[2,48] Cardiovascular disease is accountable for 24% and 30% of all deaths in persons below the age of 70 years, and 50% and 12% of people who died from CVD were of working age in Kazakhstan and Germany, respectively.[2] It has long been described that CVD is also associated with substantial productivity losses.[49,50] Besides premature deaths, the illness can impair the productive work time (absenteeism, presenteeism) or lead to early retirement for those being at working age at the time of their CVD event. While productivity losses accounted for 30% of the total CVD-related costs in Germany,[2] in Kazakhstan an estimated share of 86% of the total economic burden was attributable to productivity losses, mainly caused by the considerably higher proportion of premature deaths.[51] In our study, the value of productivity loss was used to estimate the indirect costs of CVD: the alternate strategy reduced the productivity costs by 9.5%, thereby neutralizing 70% and 180% of the required investments in screening and prevention in Germany and Kazakhstan, respectively. Disease related changes in productivity depend on many factors and the economic and social context.[49] Moreover, marked differences between some country estimates point to different sources and calculation methods.[49] An important variable is the friction period, which does not consider the full period of time a person is out of work but is limited to the time-span required to restore the initial productivity level, e.g. by replacing a worker who died from CVD.[49,52] We tested the friction period in sensitivity analyses between 3 months and 1.5 years (Supplementary material online, *Figure S6*). In both countries, the ICER of the

Screen&Prevent strategy was found significantly below the WTP threshold, thus the strategy remained cost-effective. The preference for the Screen&Prevent is corroborated by scenarios that were excluding indirect costs or focusing on costs for screening and prevention only: Screen&Prevent was still found cost-effective at the more conservative WTP threshold (Supplementary material online, *Table S2*).

Risk stratification with hsTnI selected about 5% of all individuals as high risk for CVD, and a fifth of all events actually occurred in this subgroup. On the other hand, 80% of events occurred in the low and moderate risk category and would not be eligible for preventive medication (Supplementary material online, *Table S4*). It should therefore be stressed that the effects and outcomes of any screening initiative rely on both, the management scheme and the effectiveness of subsequent prevention measures. Testing costs and effectiveness of preventive medication in bivariate sensitivity analyses over a wide range strengthens the results of the base case analysis: Screen&Prevent remains cost-saving or cost-effective in Kazakhstan and Germany, respectively (Supplementary material online, *Figure S8*).

Some authors stressed the limited or inconsistent evidence on the effectiveness of statins for primary prevention of CVD.[53] This finding was explained by several factors, such as different baseline risks or the differences in the types of outcomes reported. Before interpreting the results, it is, therefore, important to understand the impact of the uncertainty in the statin efficacy on our modelling study. For this reason, we conducted a sensitivity analysis to determine the minimum effectiveness required so that Screen&Prevent can be considered cost-effective. Although this depends heavily on the maximum willingness-to-pay, it can be concluded that Screen&Prevent is very likely to be cost-efficient if the HR of medical prevention compared to no prevention is less than 0.82 (Supplementary material online, *Figure S9*).

Cost-effectiveness analyses are comparative by nature and most commonly assess the potential benefits and costs of new strategies compared to the current situation of usual care. Despite clear guideline recommendations, risk assessment tools are still not used in about one fifth of all cases.[4] In our study, we used a do-nothing strategy as standard strategy. The underlying study only reports outcome information sorted according to hsTnI risk groups.[12] Since no information was available on how these hsTnI risk categories matched risk classes according to any other risk algorithm, a sound comparison of the hsTnI strategy to a strategy using, e.g. SCORE was not possible. Although our results may be applied to people who are not yet covered by prevention initiatives, using a do-nothing strategy as an extreme comparator is a major limitation that likely overestimated the effect of hsTnI that may be observed in practice. However, we explicitly stress the fact that our study is not recommending a strategy that is not assessing a person's individual risk for CVD. Instead, we were aiming for a first estimation of the potential cost-effectiveness of hsTnI for primary prevention of CVD: Our analysis described the boundaries to cost-effectiveness and analysed the most critical variables in different health care settings. We hope that this first and early evaluation of long-term effects and consequences of prevention strategies incorporating hs-troponin will contribute to the discussion and stimulate further research in this area. Several articles have discussed the use of hsTnI in addition to established risk-assessment tools.[10,11] While our study assessed the health economic consequences of hsTnI against a do-nothing strategy, future studies should investigate current practice, gather context-specific information, and evaluate the incremental cost-effectiveness of hsTnI-guided assessment strategies in these specific settings.

In addition, we acknowledge several further limitations. First, individual patient data were not available. Instead, event times and censorships were reconstructed from published Kaplan–Meier curves and subjects at risk. Therefore, hazard functions are approximations of the original data. The reconstruction of data based on published KM curves and its usefulness have however been discussed in a couple of articles.[28,29] Second, the HUNT study enrolled participants from the county of Nord-Trøndelag in Norway. Extrapolation to other countries like Germany or Kazakhstan should be taken with caution and may need to consider variations in ethnicity or diversity of baseline CV risk factors. Third, country specific distributions of hsTnI risk categories and their exact correlation to country specific CVD incidence rates were not available. Therefore, it was not possible to calibrate or adjust our study to country specific risks. In general, the transfer of risk profiles to other countries should always be done with caution. As discussed above, we consider our approach and conclusions to be acceptable but also emphasize that result should be regarded preliminary and that our model should be populated with country specific cohort information in future studies. Fourth, life tables were not adjusted for CVD risk and may therefore overestimate the background mortality after CVD event. Fifth, differences and high variation in treatment costs have been described.[54] Medical and productivity costs may vary within a specific disease condition depending on the manner in which the patient is managed. We only considered a part of the direct medical costs, and costs related to premature death were only considered for one year. Therefore, economic consequences associated with CVD events were underestimated thereby following a conservative approach. Sixth, the study did not account for any other measures and interventions for preventing CVD risk. All results should be interpreted against these limitations and are therefore regarded as early estimates. Subsequent studies should seek for more detailed information, and specific conditions have to be evaluated and applied to an analysis.

Conclusions

Assessing the cardiovascular risk with hsTnI in asymptomatic people and subsequently referring those at high risk to preventive means would very likely be cost-effective or cost-saving by avoiding CVD events and associated direct and indirect costs. This conclusion is retained even if only the direct costs or only the costs for screening and prevention are used. Future studies should evaluate the incremental cost-effectiveness of hsTnI-guided assessment strategies against established risk algorithms.

Supplementary material

Supplementary material is available at *European Heart Journal – Quality of Care and Clinical Outcomes* online.

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Data availability

The data underlying this article are available in the article and in its Supplementary material online.

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