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Health Policy Analysis

Comparison of Recommendations and Use of Cardiovascular Risk Equations by Health Technology Assessment Agencies and Clinical Guidelines

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A B S T R A C T

Objectives: To identify risk equations for cardiovascular diseases (CVDs) in primary and secondary prevention settings that are used or recommended by health technology assessment (HTA) organizations and in clinical guidelines (CGs). **Methods:** A targeted literature review was conducted using a two-stage search strategy. First, HTA reviews of manufacturers' drug submissions, reports from established HTA organizations (Europe, Canada, and Australia), and CGs from countries with and without HTA organizations, including the United States, were identified. Documents published between September 30, 2006 and September 30, 2016, were examined for cardiovascular risk equations, recommendations, and commentaries. Next, publications associated with risk equations and cited by HTA and CG documents were retrieved. This literature was examined to extract commentaries and risk equation study characteristics. **Results:** The review identified 47 risk equations, 25 in the primary CVD prevention setting (i.e., patients with no CVD history), including 5 for CVD prevention in diabetes and 22 solely in secondary prevention settings; 11 were identified for heart failure, 3 for stroke or transient ischemic attack, 2 for stable angina, and 11 for acute coronary syndrome or related conditions. A small set of primary prevention equations was found to be commonly used by HTAs, whereas secondary prevention equations were less common in HTA documents. CGs provided more risk equations as options than HTA documents. **Conclusions:** Although there is an abundance of risk equations developed for primary and secondary prevention, there remains a need for additional research to provide sufficient clinical and HTA guidance for risk estimation, particularly in high-risk or secondary prevention settings.

Keywords: cardiovascular disease, clinical guidelines, health technology assessment, risk equations

Introduction

Approximately half of all cardiovascular disease (CVD) deaths are due to preventable factors [1]; this indicates that risk assessment—of events in patients with no CVD history (i.e., primary prevention) or of subsequent events in patients with established CVD (i.e., secondary prevention)—is a key factor in reducing this serious global health care concern [2]. Various risk assessment tools, including risk equations, have been developed to address this need. Some clinical guidelines (CGs) recommend using these tools to assist in disease management decisions [3–8]. Most health technology assessment (HTA) agencies require economic evaluations of new treatments, and those models sometimes incorporate risk equations to predict cardiovascular (CV) events over time or estimate transition probabilities [9–21]. There are many CVD risk equations available [22], necessitating research into the optimal choices for HTA and clinical use.

Conflicts of interest: Y. Qian, M.-H. Tai, L. Kutikova, G. Villa, and C. Edwards are employees and stockholders of Amgen, Inc. M. B. Betts, S. Milev, M. Hoog, H. Jung H, and D. Milenković are current or former employees of Evidera and received research funding from Amgen, Inc. D. Milenković also receives consulting fees from UCL CRUK Cancer Trials Centre to assist in drafting a paper on the dose-response effects of cigarette smoking.

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This study was conducted to 1) identify primary and secondary CVD prevention risk equations that are most commonly used or recommended by HTA organizations or CGs and 2) compare the alignment of risk equation recommendations between HTA organizations and CGs in Europe, the United States, Canada, and Australia.

Methods

A targeted literature review of risk equations for primary and secondary risk of ischemic CVD events and mortality was conducted in two stages. Stage 1 was a search of HTA website and encompassed abstract screening, literature retrieval, and full-text examination of publicly available HTA reviews of manufacturers' drug submissions, HTA reports, and CGs in Europe (including the Czech Republic, France, Germany, Italy, Norway, Scotland, Spain, Sweden, Switzerland, and the United Kingdom), the United States, Canada, and Australia that were published between September 30, 2006 and September 30, 2016. Additional CGs were identified via the National Guideline Clearinghouse and International Guidelines Library. Stage 2 consisted of a bibliographic review of the documents identified in Stage 1 and/or retrieval of the original published sources that provided details of each risk equation.

For each risk equation that met the selection criteria presented in Table 1, information on study design, study type, cohort characteristics, risk equation covariates, risk equation outcomes, and HTA and CG organization commentaries was extracted. Full-text screening of the documents was conducted by a single investigator for each HTA or CG website, and this review and the abstracted data were validated by a second investigator.

Results

Forty-one CGs mentioned risk equations and were included in the review; 32 covered the primary prevention setting and provided guidance for healthy patients or patients at risk of CVD (2 of which were specifically for patients with dyslipidemia), 4 provided guidance for the monitoring and treatment of diabetes, and 5 were for secondary prevention populations. Twenty-two HTA submissions reported the use of risk equations in models; more than half of these were for drugs used to

Table 1 – Document selection criteria.

Criteria	Secondary sources		Primary sources
	HTA reports* and clinical guidelines	HTA drug submissions*	Risk equations
Inclusion criteria	Documents that assess the following populations: • *Primary prevention*: General population or notable populations at risk for ischemic CVD (i.e., diabetes, hypercholesterolemia, and hypertension) • *Secondary prevention*: Patients with established ischemic CVD (i.e., coronary artery disease, previous MI or stroke, angina, heart failure, or peripheral artery disease) with or without other risk factors for CVD Documents that discuss or refer to risk equations for CVD events	Submissions for statins or other cholesterol-lowering agents Submission materials including economic models that incorporate CVD risk equations HTA organization responses regarding the acceptability of CVD risk equation used and implementation in models	Risk equations or models that estimate the binary risk of ischemic CV events such as MI, stroke, TIA, heart failure, and angina, or composites of these events
Exclusion criteria	Related to risk assessment of an event other than CVD Related primarily to risk assessment and/or population of a nonischemic CV event or disease (i.e., infective or inflammatory conditions, trauma, conduction/arrhythmia conditions or events, congenital diseases, valve diseases, pericardial effusion, cardiomegaly, heart failure, or cardiomyopathy secondary to conditions other than ischemia) Related to risk assessment of a CV event or disease in a specialized subpopulation not of interest (e.g., pregnant women, patients with drug dependence, patients with cancer, patients with other non-CVDs) Related to the use of specific treatments, other than cholesterol-lowering agents, or management of patients receiving those treatments Evaluate the rate of CV events without developing a risk equation Outdated documents replaced with newer versions Not conducted in a country of interest Expert opinion articles, letters, articles without abstracts		Risk equations measuring: Acute risk of a CV event (event within the next month) Risk of hospitalization or other proxy events because of CVD as the primary outcome† Risk of nonischemic CV events as the primary outcome† Risk of CV events in specialized subpopulations

CV, cardiovascular; CVD, cardiovascular disease; HTA, health technology assessment; MI, myocardial infarction; TIA, transient ischemic attack.

* HTA bodies include the following: Pharmaceutical Benefits Advisory Committee (Australia), Canadian Agency for Drugs and Technologies in Health (Canada), Norwegian Knowledge Centre for the Health Services (Norway), Scottish Medicines Consortium (Scotland), Dental and Pharmaceutical Benefits Agency (Sweden), National Institute for Health and Care Excellence (England), Belgian Health Care Knowledge Centre (Belgium), and National Health Care Institute (the Netherlands).

† Hospitalizations, other proxy events, and nonischemic events may be included in CVD risk equations with composite outcomes.

Table 2 – List of risk equations in each setting.

Primary prevention setting	Secondary prevention setting
In CVD (20 studies) • ARIC [88] • ASSIGN [89] • Cardiovascular Life Expectancy Model [90] • CHS [91] • CUORE [92] • Dubbo Study of the Elderly [93] • EUROSTROKE [94] • Framingham CHD [23] • Framingham CVD [24] • Framingham Stroke Profile [25] • Globorisk [95] • HEART [96] • NORRISK [97] • Pooled cohort equations ASCVD [4] • PROCAM [98] • QRISK Lifetime [99] • QRISK2 [100] • Reynolds Men [101] • Reynolds Women [102] • SCORE [103] In diabetes* (5 studies) • DARTS [104] • DECODE [105] • Swedish National Diabetes Register (2008) [106] • UKPDS Outcomes Model [71] • UKPDS Risk Engine [72–74]	In heart failure (11 studies) • ADHERE CART Model [66] • American Heart Association GWTG-HF [70] • CHARM [64] • CORONA [65] • EFFECT [68] • ESCAPE [69] • Heart Failure Survival Score [61] • I-PRESERVE [62] • OPTIMIZE-HF [67] • Seattle Heart Failure Model [63] • UKPDS Outcomes Model [71] In stroke or TIA (3 studies) • ABCD [75] • UKPDS Outcomes Model [71] • UKPDS Risk Engine [72–74] In stable angina (2 studies) • ACTION [76] • Euro Heart Survey Angina Score [77] In ACS or related conditions (11 studies) • CCP [83] • GRACE Post Discharge [79] • GRACE Post Admission [80] • GRACE Risk Score [81] • GUSTO-1 [82] • PREDICT [86] • REACH [78] • TIMI-NSTEMI [84] • TIMI-STEMI [85] • UKPDS Outcomes Model [71] • UKPDS Risk Engine [72–74]

ABCD, Age, Blood Pressure, Clinical Features, and Duration; ACS, acute coronary syndrome; ACTION, Acute Coronary Treatment and Intervention Outcomes Network; ADHERE CART Model, Acute Decompensated Heart Failure National Registry Classification and Regression Tree; ASCVD, Atherosclerotic Cardiovascular Disease; American Heart Association GWTG-HF, American Heart Association Get With the Guidelines – Heart Failure; ARIC, Atherosclerosis Risk in Communities Study; CCP, Cooperative Cardiovascular Project; CHS, Cardiovascular Health Studies; CHARM, candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity; CORONA, Controlled Rosuvastatin Multinational Trial in Heart Failure; CUORE, Epidemiology and prevention of ischemic heart diseases; EFFECT, Enhanced Feedback for Effective Cardiac Treatment Study; ESCAPE, Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness; EUROSTROKE, Prediction of stroke in the general population in Europe; Framingham CHD, Framingham Coronary Heart Disease; Framingham CVD, Framingham Cardiovascular Disease; GRACE, Global Registry of Acute Coronary Event; GUSTO-1, Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries; HEART, History, EKG, Age, Risk Factors and Troponin; I-PRESERVE, Irbesartan in Heart Failure with Preserved Ejection Fraction Study; NORRISK, Norway Risk; Optimize-HF, Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure; PREDICT, Predicting Risk of Death in Cardiac Disease Tool; PROCAM, Prospective Cardiovascular Munster Study; QRISK Lifetime, QRESEARCH cardiovascular risk algorithm; QRISK2, QRESEARCH cardiovascular risk algorithm; REACH, Reduction of Atherothrombosis for Continued Health; SCORE, Systematic Coronary Risk Evaluation; TIA, transient ischemic attack; TIMI-NSTEMI, Thrombolysis in Myocardial Infarction Non-ST-elevation myocardial infarction; iiTIMI-STEMI, Thrombolysis in Myocardial Infarction ST-elevation myocardial infarction; UKPDS, United Kingdom Prospective Diabetes Study; UKPDS Outcomes Model, United Kingdom Prospective Diabetes Study Outcomes Model; UKPDS Risk Engine, United Kingdom Prospective Diabetes Study Risk Engine.

* Equations included in this section estimate the risk of first events in patients with diabetes. Two equations—the UKPDS Outcomes Model and the UKPDS Risk Engine—also appear in several secondary prevention categories because they estimate the risk of subsequent events in addition to first events in patients.

treat dyslipidemia, and the remainder were for drugs indicated for diabetes, angina, heart failure, or obesity.

From these documents, the review identified 47 risk equations; in the primary prevention setting, 25 risk equations were identified, including 5 specifically for patients with diabetes, and 22 risk equations were found for solely secondary prevention populations. Table 2 presents each risk equation by prevention setting, and Table 3 describes where each risk equation was accepted. Table 4 presents a comparison of the criticisms of risk equations across HTA and CG organizations. A full description of each risk equation study is provided in the Appendix in Supplemental Materials found at https://doi.org/10.1016/j.jval.2018.08.003. Risk equations identified from HTA organizations are discussed in detail herein, by setting.

Primary Prevention

A total of 20 CV risk equations for the primary prevention setting were identified, 14 of which were found via CGs, 1 from an HTA organization, and 5 from both HTAs and CGs. Many risk equations

Table 3 – Accepted risk equations by country*.

Risk equations	Organization type	Recommended	Likely accepted/available option/mixed findings
		Primary prevention	
Framingham equations	HTAs	PBAC	CVZ, TLV
	CGs	Australia, Canada†, Spain†	United States, Europe regional
SCORE	HTAs	KCE†, NOKC, TLV	
	CGs	Belgium, Czech Republic, Europe regional, Norway, Spain, Sweden	The Netherlands
QRISK2	HTAs	NICE	SMC
	CGs	United Kingdom	Europe regional, United States
QRISK Lifetime	CGs	United Kingdom	
ARIC	CGs		United States
ASSIGN	HTAs	SMC	
	CGs	Scotland	Europe regional
HEART	CGs	Australia	United States
CHS	CGs		United States
CUORE	CGs		Europe regional
Globorisk	CGs		Europe regional
NORRISK	HTAs		NOKC‡
Pooled cohorts equation	CGs	United States	Europe regional
PROCAM	CGs		Europe regional
Reynolds	CGs		United States
		Primary prevention in diabetes	
DARTS	CGs		United Kingdom
DECODE	CGs		United Kingdom
Swedish National Diabetes Register (2008)	CGs		United Kingdom
UKPDS	HTAs	NICE	CADTH
	CGs		Spain
		Secondary prevention in heart failure	
ADHERE CART Model	CGs	United States	
American Heart Association GWTG-HF	CGs		United States
CHARM	CGs		United States
CORONA	CGs		United States
EFFECT	CGs		United States
ESCAPE	CGs		United States
Heart Failure Survival Score	CGs		United States
I-PRESERVE	CGs		United States
OPTIMIZE-HF			United States
Seattle Heart Failure Model	CGs		United States
		Secondary prevention in stroke or TIA	
ABCD2			United Kingdom
		Secondary prevention in ACS or other CVDs	
CCP	CGs		United Kingdom
GRACE	CGs	Australia	
GUSTO-1	CGs		United Kingdom
PREDICT	CGs		United Kingdom
REACH	HTAs		CVZ, PBAC, SMC, TLV
TIMI-NSTEMI	CGs		United Kingdom
TIMI-STEMI	CGs		United Kingdom

ABCD, Age, Blood Pressure, Clinical Features, and Duration; ACS, acute coronary syndrome; ADHERE CART Model, Acute Decompensated Heart Failure National Registry Classification and Regression Tree; ARIC, Atherosclerosis Risk in Communities Study; American Heart Association GWTG-HF, American Heart Association Get With the Guidelines – Heart Failure; CADTH, Canadian Agency for Drugs and Technologies in Health; CCP, Cooperative Cardiovascular Project; CG, clinical guideline; CHARM, candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity; CUORE, Epidemiology and prevention of ischemic heart diseases; CVD, cardiovascular disease; CHS, Cardiovascular Health Studies; CORONA, Controlled Rosuvastatin Multinational Trial in Heart Failure; CVZ, Dutch Healthcare Insurance Board; EFFECT, Enhanced Feedback for Effective Cardiac Treatment Study; ESCAPE, Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness; EUROSTROKE, Prediction of stroke in the general population in Europe; GRACE, Global Registry of Acute Coronary Event; GUSTO-1, Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries; HEART, History, EKG, Age, Risk Factors and Troponin; HTA, health technology assessment; I-PRESERVE, Irbesartan in Heart Failure with Preserved Ejection Fraction Study; KCE, Belgian Health Care Knowledge Centre; NICE, National Institute for Health and Care Excellence (England and Wales); NOKC, Norwegian Knowledge Centre for the Health Services; NORRISK, Norway Risk; PBAC, Pharmaceutical Benefits Advisory Committee (Australia); PREDICT, Predicting Risk of Death in Cardiac Disease Tool; PROCAM, Prospective Cardiovascular Munster Study; OPTIMIZE-HF, Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure; REACH, Reduction of Atherothrombosis for Continued Health; SCORE, Systematic Coronary Risk Evaluation; SMC, Scottish Medicines Consortium; TIA, transient ischemic attack; TLV, Dental and Pharmaceutical Benefits Agency (Sweden); TIMI-NSTEMI, Thrombolysis in Myocardial Infarction Non-ST-elevation myocardial infarction; iiTIMI-STEMI, Thrombolysis in Myocardial Infarction ST-elevation myocardial infarction; UKPDS, United Kingdom Prospective Diabetes Study.

* No risk equations were identified from any sources in countries of interest not listed in each setting.

† Requires adjustment for use.

‡ Article on NORRISK was published on the NOKC website, without further comments.

Table 4 – Comparison of critiques of risk equations.

Risk equations	Organization type	Inappropriate geography/ generalizability	Outdated	Overestimation in specific populations	Underestimation in specific populations	Concerns in high-risk populations	Inappropriate for treated populations	Inappropriate covariates
				Primary prevention				
Framingham equations	HTAs	NICE, NOKC, SMC	NICE, NOKC	SMC	SMC	TLV, CVZ	NICE	
	CGs			Scotland, Belgium	Scotland			Scotland
SCORE	HTAs						CVZ	
QRISK2	HTAs					NICE		
				Primary prevention in diabetes				
UKPDS	HTAs		CADTH	PBAC				PBAC, CADTH
	CGs	United Kingdom, Spain	United Kingdom					
				Secondary prevention in stable angina				
ACTION	HTA	NICE						
Euro Heart Survey Angina Score	HTA	NICE						
				Secondary prevention in ACS or other CVDs				
REACH	HTAs							CVZ, TLV

ACS, acute coronary syndrome; CADTH, Canadian Agency for Drugs and Technologies in Health; ACTION, Acute Coronary Treatment and Intervention Outcomes Network; CG, clinical guideline; CVD, cardiovascular disease; CVZ, Dutch Healthcare Insurance Board; HTA, health technology assessment; NICE, National Institute for Health and Care Excellence (England and Wales); NOKC, Norwegian Knowledge Centre for the Health Services; PBAC, Pharmaceutical Benefits Advisory Committee (Australia); SMC, Scottish Medicines Consortium; SCORE, Systematic Coronary Risk Evaluation; QRISK2, QRESEARCH cardiovascular risk algorithm; TLV, Dental and Pharmaceutical Benefits Agency (Sweden); UKPDS, United Kingdom Prospective Diabetes Study.

estimate multiple outcomes. The most common outcomes were CVD-related or coronary heart disease (CHD)-related death (11 studies), stroke (11 studies), and myocardial infarction (MI; 10 studies); other outcomes included stroke-related death (5 studies), all-cause mortality (4 studies), and angina (3 studies). Fifteen studies estimated risk over 10 or more years.

Framingham equations

Three Framingham risk equations were identified during the course of the review: Framingham Heart [23], Framingham Global [24], and Framingham Stroke Profile [25], which were cited in 9 HTA documents and 23 CGs.

None of the HTA organizations explicitly recommended the use of Framingham equations; nevertheless, on the basis of the commentaries in drug reviews, it could be inferred that the Pharmaceutical Benefits Advisory Committee (PBAC; Australia), the Dental and Pharmaceutical Benefits Agency (*Tandvårds- och läkemedelsförmånsverket* [TLV]; Sweden), and the Dutch Healthcare Insurance Board (*College voor Zorgverzekeringen* [CVZ]; the Netherlands) are likely to accept them. PBAC noted concerns with their indirect use—by combining them with secondary equations rather than their direct use—or with applicability in particular patient populations, but had no general concerns regarding the validity of Framingham risk equations [26–28]. Similarly, TLV [9] had concerns with using calibration to adjust for high-risk patients, and CVZ [11] commented that the equations are not suitable for a high-risk population.

The National Institute for Health and Care Excellence (NICE), the Norwegian Knowledge Centre for the Health Services (NOKC), and the Scottish Medicines Consortium (SMC) HTA organizations found that Framingham equations were unacceptable. NICE found them to be unacceptable for use in the United Kingdom on the grounds that they are US-based [29], are not formulated to predict changes in CV risk on the basis of chemically induced changes in lipid profiles [13], and are outdated [30]. NICE recommends the use of QRESEARCH cardiovascular risk algorithm (QRISK2) over Framingham equations, UK Prospective Diabetes Study (UKPDS), or age alone [31]. NOKC did not recommend the use of Framingham equations, citing that they were old and not Norwegian [32], whereas SMC noted potential for underestimation or overestimation of risk when using the Framingham equations in patients from different social backgrounds [12].

Among the different guidelines, Belgium guidelines [33] did not recommend Framingham CHD equations, because they overpredict risk among the Belgian population. Similarly, Scottish guidelines [34] noted overprediction in populations with low observed CHD mortality and underprediction in populations with high CHD mortality; furthermore, they criticized the Framingham CHD equations for excluding certain risk factors, including obesity, physical inactivity, family history of CVD, and social status, which also led to underprediction.

Spanish guidelines [35–37] recommended the use of Framingham equations only when they are calibrated for a Spanish population (known as REGICOR). Australian guidelines [27] also recommended the use of Framingham equations. Both Canadian guidelines [8,38] recommended using Framingham equations [38] or using a modified version (double-folding the risk for a family history of premature coronary disease) [8].

In the 2016 European joint guidelines [7], the Framingham CVD equation was noted as an available option.

All American guidelines either recommended Framingham equations [39–41] or listed them as options [4,6,42–44].

SCORE

The systematic coronary risk evaluation (SCORE) risk equation was cited in 13 documents—5 CGs [7,45–48] and 8 HTA documents [12,32,33,49–53].

Among the eight HTA-identified reports, three were issued by the Belgian Health Care Knowledge Centre (KCE; Belgium), two by TLV (Sweden), and one each by NOKC (Norway), CVZ (Netherlands), and SMC (Scotland).

Two KCE reports [49,50] did not contain specific recommendations for the use of risk equations; they, however, did comment on some aspects of SCORE, proposing a modification to the risk equation to account for low-density lipoprotein and high-density lipoprotein instead of relying on total cholesterol measurement. The third report [33], which is somewhat outdated, recommended the use of SCORE.

The TLV reports [51,52] recommended SCORE as the most appropriate CVD risk equation for Sweden. The reports indicated that SCORE was more relevant to European conditions than the Framingham Heart Study, and referred to the 2004 version of the equation as particularly adapted for Swedish conditions.

The NOKC report on the Norwegian Cardiovascular Disease Model [32] referred to SCORE as the risk equation used. Considering the only criticism was lack of confidence intervals, it can be inferred that NOKC most likely finds the use of SCORE acceptable.

Finally, in an HTA drug submission [11], CVZ noted that SCORE was inappropriately used in patients already treated with hypertensives or statins, whereas an SMC drug submission [12] noted that ASSIGN, rather than SCORE, is the preferred risk equation for Scotland.

All five guidelines were European—the joint guideline [7] and four guidelines in different countries (Belgium, Czech Republic, the Netherlands, and Spain)—and recommended the use of the SCORE risk equation for predicting CVD risk in primary prevention.

QRISK2

The QRISK2 equation was referred to in six documents: three CGs and three HTA documents.

Among the HTAs, NICE recommended the use of QRISK2, but noted that it is not valid for the high-risk CV population [14,29]. SMC had no comments related to the use of QRISK2, which can be interpreted as the acceptance of QRISK2 [54].

Both the 2016 European guidelines [7] and the American guidelines for the prevention of CVD in women [6] listed QRISK2 as an available option, in addition to the preferred SCORE and Framingham risk equations, respectively. NICE explicitly recommended QRISK2 in its 2014 guidelines [31].

ASSIGN

The ASSIGN risk equation was mentioned in two CGs and one HTA drug review.

The SMC drug review [12] referred to ASSIGN as the recommended equation for Scotland, because it was developed to account for potential underestimation or overestimation of risk when using the Framingham equations in patients from different social backgrounds [34]. The European joint guidelines [7] noted that ASSIGN generally performs well.

Primary Prevention in High-Risk Groups

Five studies providing CV risk equations for use in people with diabetes were identified, with three studies indicated in CGs and two from both HTAs and CGs. Most of the outcomes estimated by the equations were MI death (four studies), MI, stroke, and stroke death (three studies each). The equations estimated CV risk over 5 or 10 years.

Three HTA organizations (the Canadian Agency for Drugs and Technologies in Health [CADTH] [55], NICE [13,31], and PBAC [10,26–28,56–59]) and two CGs (NICE [31] and Osteba [60], a Basque Country [Spain] HTA organization) commented on primary prevention risk equations for a population with diabetes, with the UKPDS risk equations being most commonly assessed.

The UKPDS (diabetes)

Most organizations [10,26–28,31,55–59] criticized the use of the UKPDS Risk Engine or Outcomes Model equations, and none explicitly endorsed either equation for a diabetic population. Criticisms of the UKPDS equations included concerns regarding generalizability to Spanish and British populations [31,60] and to contemporary patients receiving current CV treatment options [31,55] as well as the use of controversial surrogate end points, such as glycated hemoglobin, as risk predictors for CVD [55]. In Australia, PBAC commented that it overestimates CV risk in the Australian population with type 2 diabetes [59] and simply assumes a linear relationship between glycated hemoglobin and major diabetes complications [57]. PBAC rejected most uses of the UKPDS risk equations in drug submissions [10,26–28,56,57,59]. Acceptance by CADTH and NICE could be inferred, because the former published an HTA report [55] incorporating the UKPDS risk equation and the latter accepted a drug submission that incorporated UKPDS Risk Engine equations for a subgroup analysis [13].

Secondary Prevention

In our literature search, 22 risk equations for solely secondary prevention settings were identified, including risk equations for heart failure [61–71], stoke or transient ischemic attack [71–75], stable angina [76,77], and acute coronary syndrome and other CVDs [71–74,78–86]. In addition, the UKPDS Outcomes Model and Risk Engine also provide equations for estimating the risk of secondary CV events in diabetic patients with existing CVD [71–74]. Specific equations for each disease group are itemized in Table 2. Nearly all these risk equations were identified from CGs; the risk equation developed from the analysis of the REduction of Atherothrombosis for Continued Health (REACH) registry [78] was the only one for the secondary prevention setting that was referred to in HTA documents.

REACH

This risk equation was developed in 2012 because of an absence of risk equations for patients with existing CVD at the time. The model predicts secondary CV events, which are defined as MI, cerebrovascular disease, and CV death. In addition to the traditional risk factors, it includes burden of disease, lack of treatment, and geographic location related to an increased risk of subsequent CV morbidity and mortality.

REACH was cited in HTA drug reviews from CVZ (the Netherlands) [11], SMC (Scotland) [54], and TLV (Sweden) [9], but neither HTA reports nor CGs referred to REACH. None of the three HTA organizations reported explicit concerns with the use of REACH. CVZ and TLV commented on the absence of any cholesterol measure as a risk factor in REACH, which prevents modeling, for example, the treatment effect of a reduction in low-density lipoprotein-cholesterol to recurring events. SMC only reported that the model implemented REACH equations, but did not comment on its use. Therefore, for all three submissions, it can be inferred that acceptance was likely.

Discussion

This study shows that many risk equations for primary and secondary CVD prevention settings are available. Nevertheless, only

a few primary prevention equations (Framingham equations, SCORE, QRISK2, ASSIGN, and UKPDS equations) have been repeatedly used to estimate CVD risk for HTA purposes. Although the US-based Framingham Study has been at the forefront of research in CVD risk prediction, its limitations have also been acknowledged—particularly, its derivation from an exclusively white sample population and its tendency to overestimate the disease in populations with low observed CHD mortality. To mitigate these limitations, risk equations such as QRISK2, SCORE, and ASSIGN were developed as alternatives to Framingham equations.

Despite increased survival after a first CVD event (because of advances in diagnosis and treatments), risk equations in secondary prevention settings have rarely been used in HTA model submissions. REACH was the sole secondary prevention risk equation identified that was used in HTA submissions. Other existing secondary prevention equations are less established, with little or no assessment from clinical or HTA organizations. This provides a challenge in selecting secondary prevention equations, because these are more often based on shorter term, smaller cohorts, clinical trials, or less robust studies (compared with the large, long-term, prospective cohort studies on which many of the primary prevention equations are based).

CGs often cite many risk equations as options for clinical practice. For example, the 2013 American College of Cardiology/American Heart Association guideline for the management of heart failure [5] provided 11 risk equations and the 2014 NICE CG on lipid modification [31] provided 8 risk equations. In contrast, most HTA reports or drug submissions reference a couple of equations at most. When CGs cite just a couple of equations, they are typically prominent risk equations, such as the Framingham equations or SCORE.

The abundance of risk equations in the CGs is reflective of the diversity of CV risk estimation contexts. CGs may provide more options for clinicians to select an equation that best matches the demographic characteristics or clinical setting of the individual patient. It may be that CGs avoid recommending single equations because of concerns that emphasis on a particular risk assessment tool might distract from the need for patient-centered clinical judgment, or they may judge that the risk equations perform similarly and that there is insufficient evidence about the most appropriate equations for clinical management pathways. In contrast, risk equations used in HTA settings estimate population risk and prioritize generalizability to the study population, as well as the robustness of the equation. This implies that a larger selection of risk equations is more appropriate for a clinical setting, but there is no fundamental discrepancy regarding which risk equations are considered most robust or appropriate for CG versus HTA settings.

When comparing the acceptance of risk equations among HTA organizations and CGs within a country, there is alignment such that the equation recommended by the HTA is always provided as an option to be used in the CGs. Therefore, in countries where HTA guidance for risk equations is not available, recommendations from CGs may provide an adequate proxy (and vice versa). Most of the equations are considered not suitable for use in high-risk populations; therefore, there is need for calibration in these settings.

Study Limitations and Strengths

This study comes with several limitations. Because of the nature of hand-searching HTA websites and the manual review of bibliographies, a systematic literature review approach was not adopted for this study. The HTA groups differ widely on the level of detail in the reports released externally, which may create the false impression that some organizations are more or less accepting of equations than are others. In addition, our research on the comparison of HTA and CGs was available in specific countries (Australia, Belgium, Norway, Scotland, and the United Kingdom)—in some cases, we had to infer the HTA position for certain countries. This was in part due to limitations in the information released by the HTA bodies; for example, in the cases in which there was an absence of criticism or the concerns noted were only regarding how a particular equation was used, these were interpreted as an indication of acceptance, particularly if the drug submission was accepted as a whole. Finally, this study was not intended to include an assessment on equation performance, other than HTA/CG acceptance.

This study has several strengths. There is no published study examining CVD risk equations from an HTA and CG perspective. Other major strengths include the comprehensive targeted search and careful selection of studies, extensive data extraction on key characteristics of CVD risk equations, and not limiting the search to the English language.

Conclusions

There is an abundance of risk equations for both primary and secondary prevention settings; this can pose challenges in the selection of appropriate ones to be used in clinical practice or for HTA submission purposes. In primary prevention, there was clear guidance in CGs and HTAs on selection of risk equations in several countries (Australia, Belgium, Norway, Sweden, Scotland, and the United Kingdom). Popular equations, such as the Framingham equations and SCORE, were often accepted by HTA agencies, but were also subject to criticism; care should be taken to review specific criticisms by HTA authorities before selecting equations to implement in submission-bound models. Nevertheless, in high-risk populations and in secondary prevention settings, there was minimal information available to guide selection of appropriate risk equations for use in HTA submissions, although REACH was accepted by several HTAs, which could be due to the multinational nature of the study. Given the substantial burden of CV events in the secondary prevention setting, this represents a notable gap [87], and it will be important to consider the appropriateness of the populations, study dates, calibration, and covariates when selecting equations for this setting. There remains a need for additional research to provide sufficient clinical and HTA guidance for risk estimation, particularly in high-risk or secondary prevention settings.

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Supplemental Materials

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