ORIGINAL ARTICLE

The impact of addressing modifiable risk factors to reduce the burden of cardiovascular disease in Turkey

Türkiye'de kardiyovasküler hastalık yükünü azaltmada değiştirilebilir risk faktörlerine yönelmenin etkisi

Yücel Balbay, M.D.,[1] Isabelle Gagnon-Arpin, M.D.,[2] Simten Malhan, M.D.,[3] Mehmet Ergun Öksüz, M.D.,[3] Greg Sutherland, M.D.,[2] Alexandru Dobrescu, M.D.,[2] Guillermo Villa, M.D.,[4] Gülnihal Ertuğul, M.D.,[5] Mohdhar Habib, M.D.[6]

[1]Department of Cardiology University of Health Sciences, Türkiye Yüksek Ihtisas Training and Research Hospital, Ankara, Turkey
[2]The Conference Board of Canada, Ottawa, Ontario, Canada
[3]Health Management Program, Baskent University, Ankara, Turkey
[4]Economic Modeling Center, Global Health Economics, Amgen Economic Modeling Center of Excellence, Zug, Switzerland
[5]Health Policy and Reimbursement, Amgen, Istanbul, Turkey
[6]Value, Access and Policy, Amgen, Inc, Thousand Oaks, California, United States of America

ABSTRACT

Objective: Our study aimed to estimate the impact of addressing modifiable risk factors on the future burden of cardiovascular diseases (CVD) in the general population and in two high-risk populations (heterozygous familial hypercholesterolemia and secondary prevention) for Turkey.

Methods: One model investigated the impact of reaching the World Health Organization (WHO) voluntary targets for tobacco use, hypertension, type 2 diabetes, obesity and physical inactivity in the general population. Another model estimated the impact of reducing LDL-cholesterol in two high-risk populations through increased access to effective treatment. Inputs for the models include disease and risk factor prevalence rates, a population forecast, baseline CVD event rates, and treatment effectiveness, primarily derived from the published literature. Direct costs to the public health care system and indirect costs from lost production are included, although the cost of programs and pharmacological interventions to reduce risk factors were not considered.

Results: The value of reaching WHO risk factor reduction targets is estimated at US$9.3 billion over the next 20 years, while the value of reducing LDL-cholesterol is estimated at up to US$8.1 billion for high-risk secondary prevention patients and US$691 million for heterozygous familial hypercholesterolemia patients.

Conclusion: Efforts to achieve WHO risk factor targets and further lower LDL-cholesterol through increased access to treatment for high-risk patients are projected to greatly reduce the growing clinical and economic burden of CVD in Turkey.

ÖZET

Amaç: Çalışmamız, değiştirilebilir risk faktörlerinin, genel popülasyonda ve Türkiye için iki yüksek riskli popülasyonda (heterozigot ailesel hiperkolesterolemi ve sekonder önleme) gelecekteki kardiyovasküler hastalık yükü üzerindeki etkisini öngörmeyi amaçlamaktadır.

Yöntemler: Bir model, Dünya Sağlık Örgütü'nün (DSÖ) tütün kullanımı, hipertansiyon, tip 2 diyabet, obezite ve fiziksel hareketsizlik için genel popülasyondaki gönüllü hedeflere ulaşmasının etkisini araştırdı. Başka bir model, etkili tedaviye daha fazla erişim sağlayarak iki yüksek riskli popülasyonda LDL-kolesterolü azaltmanın etkisini tahmin etti. Modeller için girdiler, hastalık ve risk faktörü yaygınlık oranlarını, gelecekteki nüfus tahminini, bazal kardiyovasküler hastalık olay oranlarını ve yayınlanmış literatürden elde edilen tedavi etkinliğini içerir. Kamu sağlık bakım sistemine doğrudan maliyetler ve kayıp üretimden dolaylı oluşan dolaylı maliyetler dahil olmakla birlikte, risk faktörlerini azaltmak için programların maliyeti ve farmakolojik girişimler dikkate alınmamıştır.

Bulgular: DSÖ'nün risk faktörü azaltma hedeflerine ulaşma maliyetinin önümüzdeki 20 yılda 9,3 milyar ABD doları, yüksek riskli sekonder önleme hastaları için LDL-kolesterolü azaltma maliyetinin 8,1 milyar ABD doları ve heterozigoz ailesel hiperkolesterolemi hastaları için 691 milyon ABD doları olduğu tahmin edilmektedir.

Sonuç: DSÖ risk faktörü hedeflerine ulaşma ve yüksek riskli hastalar için tedaviye erişim yoluyla LDL-kolesterolü daha da düşürme çabalarının, Türkiye'de artan KVH klinik ve ekonomik yükünü büyük ölçüde azaltacağı tahmin edilmektedir.

Received: December 01, 2018 *Accepted:* February 13, 2019

Correspondence: Dr. Yücel Balbay. Türkiye Yüksek İhtisas Eğitim ve Araştırma Hastanesi, Kardiyoloji Kliniği, Ankara, Turkey.
Tel: +90 312 - 306 10 00 e-mail: yucelbalbay1@gmail.com

Cardiovascular diseases (CVD) account for a significant proportion of morbidity, mortality, and disability worldwide. In 2012, CVD was responsible for a third of all deaths, and by 2030 this proportion is projected to increase and greatly surpass the global burden of infectious diseases, nutritional disorders and maternal conditions combined.[1]

Abbreviations:

CeVD	*Cerebrovascular disease*
CVD	*Cardiovascular diseases*
FH	*Familial hypercholesterolemia*
HeFH	*Heterozygous familial hypercholesterolemia*
IHD	*Ischemic heart disease*
LDL-C	*Low density lipoprotein cholesterol*
NCDs	*Noncommunicable diseases*
REACH	*Reduction of Atherothrombosis for Continued Health*
SSI	*Social Security Institution*
WHO	*World Health Organization*

The burden of CVD is particularly significant in low- and middle-income countries. According to the World Health Organization (WHO), approximately 75% of CVD deaths occur in developing countries.[1] In Turkey, an upper-middle income country, noncommunicable diseases represent an estimated 86% of total deaths, while communicable diseases and injuries account for the other 14%.[2] Over the past two decades, numerous prediction models have been developed, which mathematically combine multiple predictors to estimate the risk of developing CVD—for example, the Framingham, SCORE, REACH, QRISK and models developed by the Conference Board of Canada.[3–9]

In our linked study: Modelling the Burden of Cardiovascular Disease in Turkey, we estimated the current and future burden of CVD (defined as ischemic heart disease [IHD] or cerebrovascular disease [CeVD]) in Turkey, and found that 3.4 million adults were living with CVD in 2016, and that this is estimated to increase by nearly 60% to 5.4 million by 2035.[3] In the same study, we estimated the economic burden of CVD, including direct health care costs and indirect costs from lost productivity, at US$10.2 billion in 2016, projected to increase twofold to US$19.4 billion by 2035.[3]

Several modifiable risk factors contribute to CVD prevalence and mortality. These include dyslipidemia, hypertension, diabetes, tobacco use, unhealthy diet, obesity, and physical inactivity, and high rates have been reported in the Turkish population.[10–13] Other factors, such as Turkey's increased life expectancy and aging population, have also contributed to the growing burden of CVD in the country.

To help reduce the burden of CVD, the WHO established the "Global Action Plan for the Prevention and Control of NCDs [noncommunicable diseases] 2013–2020."[14] The Plan's primary target is a reduction in the number of premature deaths from NCDs, including CVDs, of 25% by the year 2025. The global action plan also identifies eight targets for achieving this goal, five of which are directly related to CVD and include:

- 10% reduction in physical inactivity;
- 30% reduction in tobacco use;
- 25% reduction in hypertension; and
- 0% increase in diabetes and obesity.

In addition, raised total cholesterol is a major cause of disease burden in both the developed and developing world as a risk factor for IHD and stroke. In the INTERHEART study, dyslipidemia was identified as having the greatest population attributable risk for the occurrence of acute myocardial infarction worldwide.[15]

Some groups are known as being at particularly high risk for IHD and need early detection, counseling, and access to effective treatments. For example, high-risk patients include individuals with clinical atherosclerotic disease who have suffered a previous event, commonly called secondary prevention patients. Individuals with familial hypercholesterolemia (FH), which is a common genetic cause of premature IHD that exposes them to significantly high LDL-cholesterol (LDL-C) levels at an early age, are also at increased risk.

Statins are currently the treatment of choice for dyslipidemia, but studies have shown that a large proportion of high-risk patients are not reaching conventional LDL-C goals (eg, ≤2.6 mmol/L) with standard therapy.[16,17] A novel lipid-lowering treatment approach, the inhibition of pro-protein convertase subtilisin–kexin type 9 (PCSK9), was recently approved for use in some countries (as an adjunct to diet and maximally-tolerated statins ± ezetimibe) for the treatment of dyslipidemia in high-risk patients. A recent study conducted in the United States quantified the 20-year cumulative value of treating high-risk patients with PCSK9 antibody inhibitors at between US3.4 trillion and US$5.1 trillion.[18]

In the context of a high burden of chronic diseases, growing health expenditure and high preva-

lence of risk factors, policymakers and stakeholders need reliable information on the impact of strategies to reduce the burden of CVD over time. The current study fills this gap in Turkey by estimating the health and economic impact of addressing modifiable risk factors and increasing access to effective lipid-lowering treatment for high-risk populations. This study is the second of two linked studies, the first of which estimated the overall prevalence, mortality, and economic burden of CVD in Turkey.[3]

METHODS

The second study had two objectives: first, we sought to quantify the impact of reducing modifiable risk factors in the general Turkish population in accordance with WHO targets. Second, we sought to project the value of reducing LDL-C in two high-risk populations through increased access to evolocumab, one of two PCSK9 antibody inhibitor treatment options. For each model, a base case scenario and an alternative scenario were developed, and the difference between the two scenarios represents the incremental health and economic impact of reducing the relevant risk factors.

WHO risk factor reduction model

This model leverages two projections of the prevalence and economic burden of CVD in Turkey: 1) the base case scenario, detailed in our linked study;[3] and 2) the risk factor reduction scenario explained below. The cost of programs or interventions to reduce risk factors was not considered in our analysis.

The risk factor reduction scenario is based on WHO targets aimed at reducing premature mortality from noncommunicable diseases by 25% by 2025 (Table 1).[14] In this scenario, the prevalence rate of five modifiable risk factors was modeled to reach the WHO targets by 2025. The lower or maintained prevalence rates were then assumed to remain constant from 2026 to 2035.

LDL-C reduction in high-risk populations model

This model leverages two projections of the prevalence and economic burden of CVD: 1) the base case scenario, and 2) the LDL-C reduction scenario explained below. The cost of evolocumab was not considered in our analysis.

Forecasting high-risk populations

Secondary prevention patients and heterozygous familial hypercholesterolemia (HeFH) patients that could achieve target cholesterol levels with standard treatment were included in our analysis. We projected high-risk population estimates by applying the prevalence rates detailed below to Turkey population projections from the World Bank DataBank.[19]

Secondary prevention

According to results from the Turkey chronic disease and risk factor study, around 4.4% of Turkish adults have a history of either myocardial infarction, stroke or unstable angina.[10,20] Further, a Delphi panel of 13 experts in Turkey was used to classify the proportion of secondary prevention patients according to treatment status and LDL-C levels.[21] Results from the panel showed that an estimated 63% of treated secondary prevention patients in Turkey do not reach LDL-C target levels of ≤2.6 mmol/L, which is also consistent with results from the EUROASPIRE-IV study.[22]

Heterozygous Familial Hypercholesterolemia Due to uncertainty regarding the true prevalence of HeFH in Turkey, the current study applied a sensitivity analysis of HeFH global prevalence estimates ranging from 0.2% to 0.5% of the adult population aged 20 years and older,[23] although we mostly present results for the 0.5% scenario. Further, the Delphi panel of experts in Turkey has estimated that 78% of HeFH patients treated with standard lipid-lowering therapy do not achieve LDL-C levels ≤2.6 mmol/L,[21] which is consistent with a study from Béliard et al.[24] published on the topic.

Evolocumab

Treatment effectiveness

For high-risk individuals with uncontrolled LDL-C levels despite lipid-lowering therapy use, evolocumab,

Table 1. World Health Organization noncommunicable diseases risk factor reduction targets

	Diabetes	Obesity	Hypertension	Tobacco use	Physical inactivity
Target	0% increase	0% increase	25% reduction	30% reduction	10% reduction

a novel PCSK9 antibody inhibitor treatment option, has been found to further reduce LDL-C levels by 71% in secondary prevention patients[25] and 61% in HeFH patients[26] (see details at Appendix A).

CVD event rates

Baseline event rates were calculated using prediction engines for primary (Framingham)[27] and secondary (Reduction of Atherothrombosis for Continued Health [REACH])[28] CVD events. Baseline rates were then calibrated to our study populations. For secondary prevention patients, risk equations from the REACH registry were calibrated by a factor of 3.4, based on an analysis of real-world UK data by Taylor et al.[29] For HeFH patients, baseline rates were calibrated using a rate ratio of 7.1 derived from Danish population-based study.[30,31]

The impact of Evolocumab on reducing the risk of CVD events was then measured using a two-step approach. First, the relative LDL-C reduction for HeFH (61%) and secondary prevention (71%) was used to calculate absolute LDL-C reduction based on mean LDL-C levels from clinical trial patient populations: baseline LDL-C levels were 4 mmol/L for HeFH and 3.7 mmol/L for secondary prevention, which yielded absolute LDL-C reductions of 2.5 mmol/L for HeFH and 2.6 mmol/L for secondary prevention. Second, we applied rate ratios representing changes in CVD event rates associated with an absolute reduction in LDL-C levels from Cholesterol Treatment Trialists' Collaboration (CTTC), which found that a reduction of 1 mmol/L leads to a 21% reduction in rates of any major CVD event (rate ratio per mmol/L of 0.79)[32] (see details in Appendix).

Mortality rates

The share of fatal events from overall CVD events was estimated at 33%, derived from SCORE data reported in the 2016 European Guidelines on cardiovascular disease prevention in clinical practice.[33]

Forecasting the economic burden of CVD

The economic burden of CVD is a function of the event rates multiplied by the average direct cost per case, as well as productivity losses due to illness.

Direct costs

The average direct cost per IHD case reimbursed by the Social Security Institution (Sosyal Güvenlik Kurumu [SGK]) was calculated from a sample dataset of 2,728 admitted cases (ICD I20–I25) to The University of Health Sciences Türkiye Yüksek İhtisas Hospital between January and March 2016.[34] The average direct cost of hospitalized cases of CeVD was obtained from the literature.[35] An adjustment was applied to account for disease maintenance costs for non-fatal events, as per cost ratios presented by Hermus et al.,[36] and as described in our linked study. The average cost per case was converted from Turkish Lira to United States dollars (US$) using the Organisation for Economic Co-Operation and Development (OECD) purchasing power parity (PPP) adjusted exchange rate for 2014 of 1.163. In 2016, the direct cost per case was estimated at $3,399 for non-fatal events and $2,667 for fatal events. Based on expert opinion, inflation rates were not applied to the cost per case over the forecast period since the cost of health care services has remained stable in the last decade in Turkey, and is not expected to increase in the near future.

Indirect costs

Indirect costs in economic analyses are typically calculated as the value of foregone income lost due to disease. These costs can arise for several reasons, and in our model, they include costs from premature mortality, early retirement, and hospitalizations. To calculate the foregone earnings from CVD over patients' lifetime, the human capital approach was used, and leveraged existing data and estimates from the literature (see details at Appendix).

RESULTS

Impact of reaching WHO risk factor reduction targets

The population targeted by the WHO risk factor reduction scenario targets includes individuals with at least one of the modifiable risk factor of interest. In Turkey, this population is estimated based on the prevalence rate of risk factors in the adult population: physical inactivity (15.3 million), hypertension (15.6 million), obesity (13.1 million), smoking (14.3 million), type 2 diabetes (6.3 million). Based on our forecasts, the number of individuals with risk factors is projected to increase between 15%–18% by 2025, and 31%–37% by 2035, depending on the risk factor. For example, the number of individuals with hypertension is forecast to increase to 18.1 million by 2025 and 20.9 million by

2035, which represents a 16% and 34% increase respectively compared to 2016 (Table 2).

We estimated that by reaching WHO risk factor reduction targets in the adult population in Turkey, the number of CVD cases (defined as IHD and CeVD) would decrease from 5.4 million to 5 million by 2035. Over the forecast period (2016–2035), this represents 5.1 million cumulative cases averted, approximately 733,000 of which necessitate hospitalization. Mortality was also modeled to decrease in line with the reduction in CVD prevalence and incidence, with an estimated 15,701 averted deaths in 2035, and almost 190,000 averted deaths over the forecast period (Table 3).

The economic impact of the projected reduction in CVD prevalence, incidence, and mortality was estimated at $615 million in 2035, totaling $9.3 billion in cumulative savings between 2016 and 2035. Most of the savings would come from direct costs incurred by the public health care system, which is projected to save $385 million in 2035, totaling $5 billion in cumulative savings over the forecast period. Indirect cost savings to the Turkish society from increased productivity were estimated at $229 million in 2035 or $4.2 billion cumulatively over 20 years.

Impact of reducing LDL-cholesterol in high-risk populations

High-risk population 1: Secondary prevention

The first population included in our LDL-C reduction model is high-risk secondary prevention adults in Turkey, with a focus on individuals not reaching LDL-C target levels ≤2.6 mmol/L. This group was chosen to illustrate the maximum potential in reducing the burden of CVD in Turkey from treating secondary prevention patients with high LDL-C levels. In 2016, we estimated 1.5 million adults fall in this high-risk category, which is projected to increase to 1.9 million by 2035.

We found that by treating high-risk secondary prevention patients with evolocumab, 54,713 acute CVD events necessitating hospitalization could be averted by 2035, which would represent over 980,000 averted events of the 20-year forecast period. A reduction in averted events would also lead to lower mortality from CVD, which we estimated at 18,055 averted deaths in 2035, or 323,979 cumulatively over the next 20 years. The economic impact of lower CVD incidence and mortality translated into $532 million in total cost savings by 2035, totaling $8.1 billion in

Table 2. Current and projected modifiable risk factors in Turkish adults (number of individuals, in millions)

	2016 – Number of individuals (millions)	2025 – Number of individuals (millions)	2035 – Number of individuals (millions)
Hypertension	15.6	18.1	20.9
Obesity	13.1	15.5	17.9
Physical inactivity	15.3	17.6	20.0
Tobacco smoking	14.3	16.4	18.7
Type 2 diabetes	6.3	7.3	8.3

Table 3. Health and economic burden of cardiovascular disease in Turkey, by scenario

	2035			Cumulative 2015–2035
	Base case	WHO Scenario	Difference	Difference
CVD cases (number)	5,390,091	4,998,519	391,573	5,116,900
Deaths (number)	194,702	179,002	15,701	185,038
Total costs (million US$)	$8,729	$8,114	$615	$9,288
Direct costs (million US$)	$5,454	$5,068	$385	$5,049
Indirect costs (million US$)	$3,275	$3,045	$229	$4,239

WHO: World Health Organization; CVD: Cardiovascular disease; US$: United States dollar.

projected savings over the forecast period. In 2035, direct cost savings to the Turkish health care system represented around a third of total savings, reaching $173 million, while indirect cost savings to society were estimated at $359 million (Table 4).

High-risk population 2: Heterozygous familial hypercholesterolemia

The second high-risk population targeted by our LDL-C reduction model was Turkish adults with HeFH who are not reaching LDL-C levels <2.6 mmol/L. This group was included in the analysis to show the full potential for reducing the burden of CVD in Turkey from treating all HeFH patients with high LDL-C levels. Depending on the prevalence rate assumption (0.2%–0.5%), this group was estimated at between 82,223 and 205,557 adults in 2016 and is projected to increase to between 104,375 and 260,937 adults by 2035.

We estimated that by treating HeFH patients (with uncontrolled LDL-C levels) with evolocumab, up to 4,671 acute CVD events necessitating hospitalization could be averted by 2035, totaling 83,812 averted acute events over the forecast period (2016–2035). This would translate in up to 1,541 averted deaths in 2035, totaling 26,658 averted deaths over the forecast period. The cost savings associated with a reduction in acute CVD events and mortality were projected at up to $45 million in 2035. This represented $691 million in savings over the next 20 years. A third of these savings would be incurred by the public health care system in the form of direct cost savings, which were projected to reach up to $15 million by 2035. Indirect cost savings would, therefore, represent two-thirds of total savings, totaling $31 million in 2035 (Table 5).

DISCUSSION

Our study aimed to estimate the impact of addressing modifiable risk factors on the future burden of cardiovascular disease (CVD) in the general population and in two high-risk populations (heterozygous familial hypercholesterolemia and secondary prevention). We

Table 4. Health and economic impact of reducing LDL-cholesterol levels in high risk secondary prevention adults in Turkey

	2035			Cumulative 2015–2035
	Base case	LDL-C reduction scenario	Difference	Difference
CVD events (number)	142,438	87,726	54,713	981,754
Deaths (number)	47,005	28,949	18,055	323,979
Total costs (million US$)	$1,385	$853	$532	$8,098
Direct costs (million US$)	$450	$277	$173	$3,099
Indirect costs (million USS)	$935	$576	$359	$4,998

LDL-C: Low-density lipoprotein cholesterol; CVD: Cardiovascular disease; US$: United States dollar.

Table 5. Health and economic impact of reducing LDL-cholesterol levels in heterozygous familial hypercholesterolemia* adults in Turkey

	2035			Cumulative 2015–2035
	Base case	LDL-C reduction scenario	Difference	Difference
CVD events (number)	12,629	7,959	4,671	83,812
Deaths (number)	4,168	2,626	1,541	27,658
Total costs (million US$)	$123	$77	$45	$691
Direct costs (million US$)	$40	$25	$15	$265
Indirect costs (million US$)	$83	$52	$31	$427

LDL-C: Low-density lipoprotein cholesterol; CVD: Cardiovascular disease; US$: United States dollar.
*Based on 0.5% prevalence rate assumption of heterozygous familial hypercholesterolemia.

found that reaching the WHO risk factor reduction targets for arterial hypertension, tobacco smoking, type 2 diabetes mellitus, obesity and physical inactivity in the general population would avert 5.1 million cases of CVD, including 733,000 cases necessitating hospitalization, and yielded potential savings of US$7.3 billion over the 20-year forecast period.

Despite the fact that dyslipidemia is not a specific WHO voluntary target, the impact of reducing lipids is clear in cardiovascular and cerebrovascular outcomes. Indeed, increasing access to evolocumab for high-risk patients with uncontrolled LDL-C levels could avert close to 1.1 million acute CVD events necessitating hospitalization and result in up to US$8.8 billion in savings (US$691 million for HeFH patients and US$8.1 billion for secondary prevention). It is important to note that while the WHO risk reduction model included both cases necessitating hospitalization and non-hospitalized cases of CVD, the LDL-C reduction model focused only on acute events necessitating hospitalization. This also had an impact on the direct cost results since the WHO model yielded savings from averted hospitalized and non-hospitalized CVD cases, while the LDL-C model included cost savings from averted hospitalized events only.

Epidemiologic research has in fact shown that many cases of CVD are preventable through the modification, elimination or avoidance of one or several risk factors. In the Global Health Risks study published by the WHO, reducing or eliminating the top 24 modifiable risk factors could reduce by at least three quarters the number of deaths caused by the leading causes of mortality and morbidity, including CVD.[37] By addressing the top 8 risk factors for CVD, global life expectancy could be increased by approximately 5 years. Indeed, the Institute of Medicine affirmed that positive changes related to the reduction in smoking rates, improved blood lipid levels, and healthier dietary habits largely explain the reduction in CVD event rates in high-income countries.[38] Further, population-wide prevention initiatives and greater access to effective medical and pharmaceutical interventions have been identified as key drivers of these trends.[38]

According to Ford et al.,[39] several studies investigating the decline in CVD rates in developed countries have suggested that management of lifestyle risk factors and treatment each account for around 40 to 60 percent of the observed reduction. Earlier studies had suggested that risk-factor management contributes more to CVD reduction than treatment.[40–42] However, as effective pharmaceutical treatment options were developed and became more widely available, the relative contribution of treatments in the reduction of CVD was increased. For example, a report from the WHO's Multinational Monitoring of Trends and Determinants in Cardiovascular Disease concluded that treatments are responsible for most of the decline in CVD rates in developed countries.[43] Our study findings are aligned with this observation, since the cost savings generated by the reduction of risk factors according to targets yielded less savings than reducing LDL-C levels through treatment for high-risk groups.

The large savings estimated by our LDL-C reduction model can be partially explained by the very high CVD baseline risk observed in HeFH and secondary prevention patients. In fact, according to a study by Villa et al.,[31] individuals with HeFH have a 90% chance of experiencing a CVD event in their lifetime and may have up to 4 times more acute events than non-HeFH patients. As for secondary prevention, a study published by Sulo et al.[44] found that 9.6% of myocardial or stroke survivors will experience a subsequent event, and the proportion increases to 15.9% within three years.

This dire prognosis can, however, be lessened by improving diagnosis and treatment rates. In practice, the identification and diagnosis of risk factors and high-risk conditions for CVD are therefore important moderators of access to interventions. The potential impact of increased access to effective therapies for vulnerable groups can only be realized if diagnosis and treatment rates improve over time.

Given the recent rise in noncommunicable diseases in Turkey, government officials recognize the critical need for a strengthened public health system and strategy. For example, the family medicine-centered primary care is central to the delivery of health care services in Turkey and its mission includes health promotion and prevention.[45] This model of care is patient-centered, and health care professionals are tasked with promoting healthy lifestyles, working on disease prevention, and providing health education.[45] Between 2002 and 2011, it was reported that primary care visits increased from 74.8 million to 244.3 million.[46]

In light of budget increases and fund redistributions, value for money in healthcare is emerging as an important concept embraced by stakeholders. Providers, patients, payers, and policymakers all support the goal of improving outcomes and doing so as efficiently as possible. The formal process of reimbursement decision making in Turkey is well established at a National level within the Social Security Institution (SSI). Turkey has one national payer and SSI coordinates committees consisting of members from SSI, Ministry of Health, Ministry of Finance, Ministry of Development, Undersecretary of Treasury, and academics. There are two main reimbursement schemes in Turkey: the Regular Reimbursement Committee (since 2007) and the Alternative Reimbursement Committee (since 2016), and decisions from both committees are published in the Turkish Official Gazette.

Healthcare decision making is a complex and inherently multi-factorial process that includes variables other than clinical efficacy, safety, and cost-effectiveness. Goldman et al.[47] suggest a broader value framework that includes, for example, disease severity, prioritized subgroups, unmet medical need, reduced caregiver burden, patient compliance (and related factors) and innovation. Other considerations include policy drivers (national priorities) and industrial values (dynamic efficiency, generic market). Our findings should complement traditional economic analyses to inform prioritization of interventions to reduce the burden of CVD.

Although established willingness-to-pay and cost-effectiveness thresholds play an important role in healthcare policy decision-making, these economic evaluations are unable to address the issue of affordability. The affordability to successfully implement preventative interventions needs to be assessed, to estimate the financial consequences of adoption and diffusion of the new intervention within a specific health care setting and given inevitable resource constraints. In an increasingly complex decision-making landscape, it is critical that government and industries develop partnerships to identify and prioritize healthcare adoption in order to facilitate sustainable and evidence-driven resource allocation. Value-based healthcare initiatives and managed entry agreements are examples of these types of innovative partnerships.

Our study further supports Turkey's efforts to manage noncommunicable diseases such as CVD, by quantifying the large health and economic impact that could result from addressing the most important modifiable risk factors and increasing access to effective treatment options for high-risk populations.

Limitations

This report makes use of the best available information to forecast the prevalence and economic burden of CVD in Turkey. While every effort was made to maximize the accuracy of these forecasts, certain limitations in the data sources and modeling assumptions are worth noting. In our WHO risk factor reduction model, the prevalence of conditions and risk factors are mostly derived from self-reported national survey data and the literature. Since studies have shown that respondents tend to significantly understate their weight and physical activity in self-reported surveys, the data may be underestimating the prevalence of these risk factors.

In our study, the prevalence of risk factors is assumed to remain constant over the forecast period, although the longitudinal Turkey Adult Risk Factor Study (TEKHARF) could have been used to derive historical data on risk factor progression in Turkey.[48]

In our LDL-C reduction model, there is likely a minor overlap between the HeFH population who have had a prior event (therefore who are considered secondary prevention) and the regular secondary prevention population.

Our study featured two separate models: the WHO risk factor reduction model and the LDL-C reduction model, and caution should be used when comparing their respective results. For one, the WHO model included both acute CVD cases (necessitating hospitalization) and non-hospitalized cases, while the LDL-C model included acute hospitalized events only. Furthermore, the WHO model used dichotomous risk factor outcomes (for example regular tobacco smoking compared to non-smoking), while the LDL-C model used a continuous measure of blood lipid levels which likely yielded more favorable results.

Another limitation of the study is that it does not factor in the cost to implement interventions to address modifiable risk factors. Applying the cost of treatment to the incremental cost savings generated by the model would therefore modestly offset the expected direct cost savings.

Although the qualitative context is presented regarding data and modeling assumptions uncertainty, formal sensitivity analyses were not conducted. As noted in other published cardiovascular burden of illness studies, further data generation is critical to inform, validate and to test the robustness of the burden of disease and the impact of addressing modifiable risk factors estimates.[49,50]

Conclusion

Turkey's health care system is facing important challenges, such as a growing burden of chronic diseases, high prevalence of risk factors and increasing health expenditure. Our study showed that by reaching the WHO risk factor reduction targets and increasing access to effective LDL-C lowering treatment for high-risk groups, the burden of CVD can be greatly reduced over the next 20 years. Efforts undertaken as part of a greater focus on public health and primary care, including policies and cross-sector interventions, are important allies in the fight against noncommunicable diseases in Turkey.

Peer-review: Externally peer-reviewed.

Conflict-of-interest: None.

Authorship contributions: Concept: Y.B., I.G.A., S.M., M.E.Ö., G.E., M.H.; Design: Y.B., I.G.A., S.M., M.E.Ö., G.E., M.H.; Supervision: Y.B., I.G.A., S.M., M.E.Ö., G.E., M.H.; Materials: Y.B., I.G.A., S.M., M.H.; Data: Y.B., S.M., I.G.A.; Analysis: Y.B., I.G.A., S.M., M.E.Ö., A.D., G.V., M.H.; Literature search: Y.B., I.G.A., S.M., M.E.Ö., A.D., M.H.; Writing: Y.B., I.G.A., S.M., M.E.Ö., G.V., M.H.; Critical revision: Y.B., I.G.A., S.M., M.E.Ö., A.D., G.V., G.E., M.H.

REFERENCES

1. WHO. Cardiovascular diseases (CVDs). 2015. Available at: http://www.who.int/cardiovascular_diseases/en/. Accessed February 22, 2016.
2. WHO. Noncommunicable diseases country profiles, 2014 - Turkey. 2014.
3. Balbay Y, Gagnon-Arpin I, Malhan S, Öksüz ME, Sutherland G, Dobrescu A, et al. Modeling the burden of cardiovascular disease in Turkey. Anatol J Cardiol 2018;20:235–40.
4. Anderson KM, Wilson PW, Odell PM, Kannel WB. An updated coronary risk profile. A statement for health professionals. Circulation 1991;83:356–62. [CrossRef]
5. Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of coronary heart disease using risk factor categories. Circulation 1998;97:1837–47. [CrossRef]
6. Conroy RM, Pyörälä K, Fitzgerald AP, Sans S, Menotti A, De Backer G, et al; SCORE project group. Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. Eur Heart J 2003;24:987–1003. [CrossRef]
7. Hippisley-Cox J, Coupland C, Robson J, Brindle P. Derivation, validation, and evaluation of a new QRISK model to estimate lifetime risk of cardiovascular disease: cohort study using QResearch database. BMJ 2010;341:c6624. [CrossRef]
8. Bounajm F, Dinh T, Thériault L. Améliorer les habitudes de vie : des retombées importantes pour la santé et l'économie du Québec. The Conference Board of Canada. 2014. Available at: https://www.conferenceboard.ca/e-library/abstract.aspx?did=6647. Accessed August 31, 2018.
9. Thériault L, Stonebridge C, Browarski S. The Canadian Heart Health Strategy: Risk Factors and Future Cost Implications. The Conference Board of Canada. 2010. Available at: https://sencanada.ca/content/sen/committee/412/SOCI/Briefs/2015-05-07ReportCdnCardiovascularSociety-AddInfoConferenceBoardofCanada_e.pdf. Accessed, February 5, 2019.
10. Ünal B, Ergör, G., Dinç Horasan, G., Kalaça, S., Sözmen, K. Chronic Diseases and Risk Factors Survey in Turkey. Ankara: Anıl Matbaa Ltd. Şti; 2013. p. 68-89.
11. Kılıçkap M, Barçın C, Göksülük H, Karaaslan D, Özer N, Kayıkçıoğlu M, et al. [Data on prevalence of hypertension and blood pressure in Turkey: Systematic review, meta-analysis and meta-regression of epidemiological studies on cardiovascular risk factors]. [Article in Turkish] Turk Kardiyol Dern Ars 2018;46:525–45.
12. World Health Organization. WHO Global Health Observatory Data Repository [online database]. 2013.
13. Yılmaz MB, Kılıçkap M, Abacı A, Barçın C, Bayram F, Karaaslan D, et al. [Temporal changes in the epidemiology of diabetes mellitus in Turkey: A systematic review and meta-analysis]. [Article in Turkish] Turk Kardiyol Dern Ars 2018;46:546–55.
14. WHO. NCD Global Monitoring Framework - Ensuring progress on noncommunicable diseases in countries [press release]. 2013
15. Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, Lanas F, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. Lancet 2004;364:937–52. [CrossRef]
16. Perez de Isla L, Alonso R, Watts GF, Mata N, Saltijeral Cerezo A, Muñiz O, et al. Attainment of LDL-Cholesterol Treatment Goals in Patients With Familial Hypercholesterolemia: 5-Year SAFEHEART Registry Follow-Up. J Am Coll Cardiol 2016;67:1278–85. [CrossRef]
17. Lotufo PA, Santos RD, Figueiredo RM, Pereira AC, Mill JG, Alvim SM, et al. Prevalence, awareness, treatment, and control of high low-density lipoprotein cholesterol in Brazil: Baseline of the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil). J Clin Lipidol 2016;10:568–76. [CrossRef]
18. Jena AB, Blumenthal DM, Stevens W, Chou JW, Ton TGN,

Goldman DP. Value of improved lipid control in patients at high risk for adverse cardiac events. Am J Manag Care 2016;22:e199-207.

19. The World Bank. DataBank: Population estimates and projections. Available at: http://databank.worldbank.org/data/reports.aspx?source=Health%20Nutrition%20and%20Population%20Statistics:%20Population%20estimates%20and%20projections. Accessed July 15, 2016.
20. Yusuf S, Islam S, Chow CK, Rangarajan S, Dagenais G, Diaz R, et al. Use of secondary prevention drugs for cardiovascular disease in the community in high-income, middle-income, and low-income countries (the PURE Study): a prospective epidemiological survey. Lancet 2011;378:1231–43. [CrossRef]
21. Disease Management Process in Hyperlipidemia in Turkey: The Results of a Delphi Panel. Istanbul, Turkey; May 2016.
22. Tokgözoğlu L, Kayıkçıoğlu M, Altay S, Aydoğdu S, Barçın C, Bostan C, et al. [EUROASPIRE-IV: European Society of Cardiology study of lifestyle, risk factors, and treatment approaches in patients with coronary artery disease: Data from Turkey]. [Article in Turkish] Turk Kardiyol Dern Ars 2017;45:134–44.
23. Nordestgaard BG, Chapman MJ, Humphries SE, Ginsberg HN, Masana L, Descamps OS, et al. Familial hypercholesterolaemia is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease: consensus statement of the European Atherosclerosis Society. Eur Heart J 2013;34:3478-90a.
24. Béliard S, Carreau V, Carrié A, Giral P, Duchêne E, Farnier M, et al. Improvement in LDL-cholesterol levels of patients with familial hypercholesterolemia: can we do better? Analysis of results obtained during the past two decades in 1669 French subjects. Atherosclerosis 2014;234:136–41. [CrossRef]
25. Raal FJ, Stein EA, Dufour R, Turner T, Civeira F, Burgess L, et al. PCSK9 inhibition with evolocumab (AMG 145) in heterozygous familial hypercholesterolaemia (RUTHERFORD-2): a randomised, double-blind, placebo-controlled trial. Lancet 2015;385:331–40. [CrossRef]
26. Robinson JG, Nedergaard BS, Rogers WJ, Fialkow J, Neutel JM, Ramstad D, et al. Effect of evolocumab or ezetimibe added to moderate- or high-intensity statin therapy on LDL-C lowering in patients with hypercholesterolemia: the LAPLACE-2 randomized clinical trial. JAMA 2014;311:1870–82. [CrossRef]
27. D'Agostino RB sr, Vasan RS, Pencina MJ, Wolf PA, Cobain M, Massaro JM, et al. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. Circulation 2008;117:743–53. [CrossRef]
28. Wilson PW, D'Agostino R sr, Bhatt DL, Eagle K, Pencina MJ, Smith SC, et al. An international model to predict recurrent cardiovascular disease. Am J Med 2012;125:695-703.e1. [CrossRef]
29. Taylor B, Lothgren M, Villa G, Lindgren P, Van Hout B, Mark D. Differences Between Observed and Predicted Cardiovascular Event Rates Using the Framingham and REACH Equations: The Case of High-intensity Statin Users in the United Kingdom. Circulation 2015;132:A18114.
30. Benn M, Watts GF, Tybjaerg-Hansen A, Nordestgaard BG. Familial hypercholesterolemia in the danish general population: prevalence, coronary artery disease, and cholesterol-lowering medication. J Clin Endocrinol Metab 2012;97:3956–64.
31. Villa G, Wong B, Kutikova L, Ray KK, Mata P, Bruckert E. Prediction of cardiovascular risk in patients with familial hypercholesterolaemia. Eur Heart J Qual Care Clin Outcomes 2017;3:274–80. [CrossRef]
32. Cholesterol Treatment Trialists' (CTT) Collaboration, Baigent C, Blackwell L, Emberson J, Holland LE, Reith C, et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. Lancet 2010;376:1670–81. [CrossRef]
33. Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL, et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practiceThe Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts)Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). Eur Heart J 2016;37:2315–81. [CrossRef]
34. Data from the billing system of the University of Health Sciences Türkiye Yüksek Ihtisas Hospital, 2016.
35. Asil T, Celik Y, Sut N, Celik AD, Balci K, Yilmaz A, et al. Cost of acute ischemic and hemorrhagic stroke in Turkey. Clin Neurol Neurosurg 2011;113:111–4. [CrossRef]
36. Hermus G, Stonebridge C, Dinh T, Didic S, Thériault L. Reducing the Health Care and Societal Costs of Disease: The Role of Pharmaceuticals. CASHC; 2013.
37. WHO. Global health risks: mortality and burden of disease attributable to selected major risks. Geneva: World Health Organization; 2009.
38. Institute of Medicine (US) Committee on Preventing the Global Epidemic of Cardiovascular Disease: Meeting the Challenges in Developing Countries; Fuster V, Kelly BB, eds. Promoting Cardiovascular Health in the Developing World: A Critical Challenge to Achieve Global Health. Washington (DC): National Academies Press (US); 2010.
39. Ford ES, Ajani UA, Croft JB, Critchley JA, Labarthe DR, Kottke TE, et al. Explaining the decrease in U.S. deaths from coronary disease, 1980-2000. N Engl J Med 2007;356:2388–98. [CrossRef]
40. Beaglehole R. International trends in coronary heart disease mortality and incidence rates. J Cardiovasc Risk 1999;6:63–8.
41. Capewell S, Beaglehole R, Seddon M, McMurray J. Explanation for the decline in coronary heart disease mortality rates in Auckland, New Zealand, between 1982 and 1993. Circulation 2000;102:1511–6. [CrossRef]
42. Unal B, Critchley JA, Capewell S. Explaining the decline in coronary heart disease mortality in England and Wales between 1981 and 2000. Circulation 2004;109:1101–7. [CrossRef]

43. Davies AR, Smeeth L, Grundy EMD. Contribution of changes in incidence and mortality to trends in the prevalence of coronary heart disease in the UK: 1996 2005. Eur Heart J 2007;28:2142–7. [CrossRef]
44. Sulo G, Vollset SE, Nygård O, Igland J, Egeland GM, Ebbing M, et al. Trends in acute myocardial infarction event rates and risk of recurrences after an incident event in Norway 1994 to 2009 (from a Cardiovascular Disease in Norway Project). Am J Cardiol 2014;113:1777–81. [CrossRef]
45. Dundar M, Uzak AS, Karabulut Y. Healthcare in overview of Turkey. EPMA J 2010;1:587–94. [CrossRef]
46. Atun R, Aydın S, Chakraborty S, Sümer S, Aran M, Gürol I, et al. Universal health coverage in Turkey: enhancement of equity. Lancet 2013;382:65–99. [CrossRef]
47. Goldman D, Lakdawalla D, Philipson TJ, Yin W. Valuing health technologies at NICE: recommendations for improved incorporation of treatment value in HTA. Health Econ 2010;19:1109–16. [CrossRef]
48. Institute for Health Metrics and Evaluation. Turkey Adult Risk Factor Study 2008. Available at: http://ghdx.healthdata.org/record/turkey-adult-risk-factor-study-2008. Accessed April 19, 2018.
49. Sacco RL, Roth GA, Reddy KS, Arnett DK, Bonita R, Gaziano TA, et al. The Heart of 25 by 25: Achieving the Goal of Reducing Global and Regional Premature Deaths From Cardiovascular Diseases and Stroke: A Modeling Study From the American Heart Association and World Heart Federation. Circulation 2016;133:e674-690. [CrossRef]
50. Damen JA, Hooft L, Schuit E, Debray TP, Collins GS, Tzoulaki I, et al. Prediction models for cardiovascular disease risk in the general population: systematic review. BMJ 2016;353:i2416. [CrossRef]

Keywords: Cardiovascular diseases; heart diseases; hyperlipidemias; public health; risk factors.

Anahtar sözcükler: Kardiyovasküler hastalıklar; kalp hastalıkları; hiperlipidemiler; halk sağlığı; risk faktörleri.