Association of country economy and socioeconomic factors on risk factor control for primary prevention of cardiovascular disease in patients with diabetes mellitus: Insights from the DISCOVER study

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Original Article

ABSTRACT

Background: We sought to describe global patterns in achievement of risk factor control for primary prevention in patients with T2D and explore the association of country's GNI/capita with risk factor control.

Methods: The DISCOVER study is a prospective, observational study of patients with T2D from 38 countries enrolled at initiation of second-line glucose-lowering therapy. We examined achievement of risk factor control (glycosylated hemoglobin <7%, blood pressure <140/90 mmHg, prescription of a statin) at 3 years among those without optimal control at baseline. Countries were stratified by gross national income (GNI)/capita, from 2017). We examined the impact of country GNI/capita with achievement of risk factor control.

Findings: Our cohort included 9613 patients with T2D and without baseline cardiovascular disease (mean age 57.2 ± 8.7 years, 47.9% women). At baseline, 6354/7646 patients (83.1%) had suboptimal glucose control, 3449/9200 patients (37.5%) had suboptimal BP control, and 2800/4221 patients (66.7%) were not on an appropriate statin (sample sizes differed due to missing covariate data). Optimal control at 3 years of follow-up was achieved in 41% (glucose), 56% (blood pressure), and 29% (statins) of patients. There was significant variability in achievement of risk factor control across countries but no association between country GNI/capita with achievement of risk factor control (p > 0.08 for all).

Interpretation: In a global, prospective study of patients with T2D, we found that cardiovascular risk factor control achievement was suboptimal despite 3 years of follow-up in specialized health care systems. Neither country-level nor patient-level socioeconomic factors fully explained this finding.

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1. Introduction

Type 2 diabetes (T2D) threatens patients of all races and socioeconomic,1 and T2D is now being characterized as a global epidemic due to its wide reach and rising trajectory.2 Key risk factors such as blood pressure and cholesterol management interact with glycemia to significantly elevate cardiovascular morbidity and mortality. As such, it is imperative to have an international focus on cardiovascular risk factor control so as to reduce the global cardiovascular morbidity and mortality associated with T2D.3 Prior studies have shown that fewer than half of patients with T2D in the US meet the recommended standards for cardiovascular risk factor control for primary prevention,4,5 with similar trends across other countries6 including United Kingdom,7 Sweden,8 Scotland,9 Germany,10 and Australia.11 Unfortunately, despite evidence showing that cardiovascular risk factor control reduces the risk of microvascular and macrovascular events,12–16 and strong guideline statements,17–20 there has been little improvement in this regard.

Multiple factors including considerations at the level of the patient (comorbidities, adherence, financial barriers),21 provider (gaps in quality of care),22–25 and health care system (lack of resources, access to care)24 may contribute to suboptimal cardiovascular risk factor control in T2D. While prior studies have primarily focused on patient and provider factors, different health systems in each country face unique challenges, which could have a marked impact on the ability of patients to achieve cardiovascular risk factor control. One such factor is a country’s economic strength, which likely plays an important role in assuring the financial sustainability of its health care system. In this study, we sought to determine if there is an association between a country’s economic resources (assessed with gross national income [GNI/capita]) and achievement of cardiovascular risk factor control in a cohort of patients with T2D and no known atherosclerotic cardiovascular disease (ASCVD; i.e., primary prevention).

2. Methods

Study Population. Our analytic cohort was derived from patients enrolled in the DISCOVER study (ClinicalTrials.gov identifiers: NCT02322762, Japan NCT02226822) – a global, prospective, longitudinal, observational study of patients with T2D enrolled at initiation of second-line glucose-lowering therapy.26 For each country in the DISCOVER study, study sites were selected by the DISCOVER committee, with the aim of obtaining a sample that was representative of the population. Prior to the selection of the study sites, data relating to the management of T2D (such as the types of practices visited by people with T2D, the specialties of the treating physicians, the geographical and rural or urban distribution of practices, and the source of funding of practices) were collated for each country from peer-reviewed articles, reports published by international healthcare organizations and insights from national experts. A list of sites that matched these characteristics as closely as possible was then produced for each country, and these sites were invited to participate in DISCOVER. Within each study site consecutive adult patients were invited to participate from December 2014 to June 2016 across 38 countries and followed prospectively for 3 years, with data collected using a standardized electronic case report forms. Patients with type 1 diabetes, end-stage renal disease on dialysis, renal transplant, and pregnancy were excluded. As our goal was to examine achievement of risk factor control for primary prevention, we excluded patients with known ASCVD (coronary artery disease, stroke, peripheral arterial disease) and patients <40 or >75 years of age, as primary prevention guidelines differ in these age extremes (e.g., conservative glucose control and no statins may be appropriate for older people). Furthermore, we focused our analysis on those patients who were not at goal for risk factor control at baseline—and examined achievement of risk factor control at 3-year follow-up. Country income was defined as GNI/capita for the year 2017 from the annual World Bank report (Supplementary Table 1).26 The DISCOVER study protocol was approved by clinical research ethics committees in each participating country and the relevant institutional review boards at each site. The protocol complies with the Declaration of Helsinki, the International Conference on Harmonisation of Good Clinical Practice, and the local regulations for clinical research. All study participants provided written informed consent.

Definition of Risk Factor Control. We examined the following 3 cardiovascular risk factors: glucose, blood pressure (BP), and lipids. Glucose control was defined as glycosylated hemoglobin (HbA1C) <7%. Blood pressure control was defined as blood pressure <140/90 mmHg. Lipid control was defined as being on an appropriate statin, which was defined as either being on any statin or being on a high intensity statin if the patient had a cardiovascular risk enhancer (low density lipoprotein–cholesterol >160 mg/dL, glomerular filtration rate <60 mL/min/1.73 m², systolic blood pressure >160 mmHg, or current smoking), per latest guidelines from American College of Cardiology and European Society of Cardiology.26,27 All patients in our cohort had T2D and hence were at an above average risk of atherosclerotic cardiovascular disease. Moreover, the presence of any risk enhancer, elevates the risk. Hence, we deemed any statin therapy in patients without risk enhancers, and high intensity statin therapy for patients with any risk enhancer to be adequately controlled. As we examined each of these risk factors separately, we had a different cohort for each risk factor.

Statistical Analysis. To examine the association of country GNI/capita on achievement of risk factor control at 3 years (among patients not at goal at baseline), we fit hierarchical logistic regression models for achievement of each of the 3 risk factors (glucose, BP, lipids) with a fixed effect for country GNI/capita (as a continuous variable). Patient-level socioeconomic factors of age, sex, education level (≥7-years), employment status (employed vs. retired vs. unemployed), living alone, and insurance status (private vs. public vs. none) were also included in the model, as they have been associated with poorer adherence and delays in treatment.8,28,29 As the association of patient socioeconomic factors and risk factor control could differ across countries with different incomes, we examined interactions of each of these socioeconomic factors with country-level GNI/capita. As interim cardiovascular events would be expected to impact the aggressiveness by which risk factors are controlled, we performed a sensitivity analysis excluding patients with interim ASCVD events.

Country was included as a random effect to account for clustering of patients within countries, and the variability in risk factor control across countries was quantified using median odds ratios (MOR). An MOR estimates the difference in odds of a patient with similar sociodemographic factors achieving risk factor control if from one random country versus another. An MOR of 1 indicates no country-level variation in risk factor control, with higher MORS representing increased variability in risk factor control due to country independent of patient sociodemographic factors. We also examined the proportion of patients at goal for risk factor control at baseline and at 3 years across countries stratified by increasing GNI/capita. For these analyses we excluded countries with less than 10 patients in the cohort to provide more stable estimates of risk factor control. All analyses were performed with SAS version 9.4 (SAS Institute, Cary, NC), and two-sided p-values < 0.05 were considered statistically significant.
3. Results

Patient Cohort. Among 15,983 patients with T2D from 38 countries enrolled in the DISCOVER study from 2014 to 2016, we excluded 1292 patients from China due to new regulations on data privacy released during the study, 1559 patients with known ASCVD at baseline, 1930 patients <40 or >75 years of age. Of the remaining 11,202 patients with T2D and no known ASCVD from 37 countries, 9613 (85.8%) had follow-up at 3 years, which comprised our primary analytic cohort (Fig. 1). Mean age was 57.2 ± 8.7 years, 47.9% were women, 18.5% had <7 years of formal education, and 26% had no medical insurance (Table 1). Patients excluded due to missing follow-up data were more likely to be current smokers, live alone, and have public insurance (Supplemental Table 1). GNI/capita among the 37 countries in DISCOVER ranged from $6560 (India) to $85,900 (Kuwait) (Supplement Table 2).

Achievement of Risk Factor Control. At study enrollment, 6354/7646 patients (83.1%) had suboptimal glucose control, 3449/9200 patients (37.5%) had suboptimal BP control, and 2800/4221 patients (66.7%) were not on appropriate statin (sample sizes differed due to missing covariate data). Among patients not at goal at baseline, 40.8% achieved optimal glucose control, 55.5% achieved BP control, and 28.6% were prescribed an appropriate statin at 3 years, respectively. Among patients with complete data, 177/3832 (4.6%) had optimal control of all 3 risk factors at baseline, and 436/2488 (17.5%) had optimal control of all 3 risk factors at study end. There was moderate variation in risk factor control at baseline and at 3 years, but no apparent unadjusted association of risk factor control with country GNI/capita (Fig. 2).

In the hierarchical models, there was no significant association between country GNI/capita and odds of achieving risk factor control at 3 years for any of the 3 measures (glucose: OR 0.99, 95% CI 0.94–1.04; BP: OR 0.96, 95% CI 0.91–1.01; lipids: OR 1.02, 95% CI 0.96–1.09). Among patient-level factors, having no insurance (vs. having insurance) was associated with lower odds of achieving goal HbA1c but a higher odds of being on appropriate statin, and living alone (vs living with family) was associated with lower odds of being on appropriate statin (Fig. 3). There were no significant interactions between any of the patient-level socioeconomic factors and country GNI/capita for achieving glucose control and appropriate statin (p > 0.1 for all). For achievement of BP goal, there was a marginally significant interaction between country GNI/capita and living status (p = 0.05), where higher GNI/capita was associated with a slightly lower odds of achievement of BP control among patients living alone but not among those not living alone (Supplementary Figure 1). The MORs for a patient achieving control of glucose, BP, and appropriate statin were 1.56, 1.48, and 1.55, respectively, indicating moderate country-level variation independent of patient-level socioeconomic factors and country GNI/capita. Finally, in a sensitivity analysis excluding 385 patients who

| Table 1 | Patient characteristics at baseline. |
|---------|-------------------------------------|
| Patient Factors | Analytical Cohort n = 9613 |
| Age (years) [mean ± SD] | 57.2 ± 8.7 |
| Women | 4605 (47.9%) |
| Current Smoker | 1193 (12.7%) |
| Current Alcohol Drinker | 2053 (22.5%) |
| Chronic Kidney Disease | 360 (3.8%) |
| Body Mass Index (kg/m²) [Mean ± SD] | 29.5 ± 5.9 |
| Time since T2D diagnosis (years) [Mean ± SD] | 5.6 ± 5.0 |
| Hypertension | 4928 (51.3%) |
| Hyperlipidemia | 4414 (46.0%) |
| Respiratory Disease | 303 (3.2%) |
| Depression | 344 (3.6%) |
| Education level | |
| None | 257 (2.9%) |
| 1–6 years | 1381 (15.6%) |
| 7–13 years | 4427 (49.9%) |
| Higher education | 2803 (31.6%) |
| Lives alone | 693 (7.6%) |
| Employed | 4633 (50.7%) |
| Retired | 1652 (18.1%) |
| Medical insurance | |
| None | 2358 (26.0%) |
| Private Insurance | 1348 (14.8%) |
| Public Insurance | 5108 (56.2%) |

T2D – Type 2 Diabetes.
Fig. 2. Country level variability for risk factors control at 3 years. A. glucose; B. blood pressure; C. appropriate statin. For statins, Costa Rica, Denmark, Japan, Oman, and Bahrain were excluded, as <10 patients could be assessed.
**Association of Socioeconomics with Risk Factor Control**

### A. Patients at Goal HbA1C (%)

- **Country GNI/Capita per $5000 Increase** 0.99 (0.94-1.04)
- **≥7 years of education** 1.23 (1.02-1.48)
- **Working Status (REF: Employed)**
  - Retired 0.86 (0.71-1.05)
  - Unemployed 0.93 (0.78-1.12)
  - Lives Alone 1.04 (0.83-1.30)
- **Medical Insurance (REF: Private)**
  - Public 0.76 (0.61-0.94)
  - Mixed 0.81 (0.55-1.19)
  - None 0.64 (0.51-0.80)
- **Age per 10-year Increase** 1.16 (1.06-1.26)
- **Female Sex** 1.03 (0.89-1.19)

### B. Patients at Goal Blood Pressure (%)

- **Country GNI/Capita per $5000 Increase** 0.96 (0.91-1.01)
- **≥7 years of education** 0.99 (0.79-1.24)
- **Working Status (REF: Employed)**
  - Retired 1.06 (0.83-1.35)
  - Unemployed 1.02 (0.80-1.29)
  - Lives Alone 1.16 (0.86-1.57)
- **Medical Insurance (REF: Private)**
  - Public 1.00 (0.75-1.34)
  - Mixed 0.80 (0.46-1.41)
  - None 0.88 (0.65-1.20)
- **Age per 10-year Increase** 0.98 (0.88-1.10)
- **Female Sex** 0.98 (0.81-1.19)

### C. Patients on Appropriate Statin (%)

- **Country GNI/Capita per $5000 Increase** 1.02 (0.96-1.09)
- **≥7 years of education** 1.00 (0.69-1.45)
- **Working Status (REF: Employed)**
  - Retired 1.16 (0.76-1.77)
  - Unemployed 0.83 (0.56-1.23)
  - Lives Alone 0.39 (0.21-0.72)
- **Medical Insurance (REF: Private)**
  - Public 1.05 (0.69-1.59)
  - Mixed 1.06 (0.47-2.40)
  - None 1.78 (1.08-2.96)
- **Age per 10-year Increase** 0.87 (0.73-1.05)
- **Female Sex** 0.70 (0.51-0.96)

*Fig. 3.* Association of patient factors with achievement of risk factor control at 3 years.
developed ASCVD during follow-up, results were consistent with the primary analysis (Supplementary Figure 2).

4. Discussion

Cardiovascular risk factor control can be particularly powerful for reducing the risk of ASCVD in patients with T2D. For example, half of the decline in deaths due to ASCVD in the US over the past 20 years has been attributed to risk factor control, with a much smaller percentage attributed to specialized treatments.10 In a global, prospective study of nearly 10,000 patients from 37 countries with T2D and no known ASCVD, we found that a substantial proportion of patients did not have optimal cardiovascular risk factor control at enrollment, but more importantly, achievement of risk factor control after 3 years of follow-up was sub-optimal. While there was moderate variation across countries in the percentage of patients who achieved risk factor control, country GNI/capita (one measure of a country’s economic resources) was not associated with better (or worse) achievement in risk factor control. Furthermore, while a few significant associations emerged with some patient-level factors, there were no factors consistently associated with control across the risk factors examined. Our results underscore the urgent need to develop and implement policies aimed at improving risk factor control across different cultures and healthcare systems, as even in patients receiving specialized care for T2D cardiovascular risk factor control is sub-optimal.

Countries with strong economies have the resources to invest in healthcare infrastructure, which, in theory, should translate into better risk factor control. The reason we did not identify any association between country-level economic resources and risk factor control is likely to be multifactorial. First, healthcare spending can vary substantially across countries with similar resources.31,32 Second, the efficiency and effectiveness of the healthcare system varies across countries with similar healthcare spending. For example, the U.S. spends approximately twice as much on healthcare as other high income countries, yet has the lowest life expectancy.33 Notably, the cultural, geographical, and political influences that contributed to the evolution of the healthcare systems of various countries can markedly impact the care and outcomes of patients. Finally, while a country may have sufficient economic resources, appropriate healthcare spending, and efficient healthcare systems, the variability in individual economic factors may be different among patients within the same country. All of these factors (and more) likely contribute to the lack of association between country-level economic resources and cardiovascular risk factor goal attainment.

At an individual level, low socioeconomic status has been associated with decreased survival,12 most likely driven in part by both poorer cardiovascular risk factor control and unhealthy behaviors (e.g., smoking, lack of exercise).13,14 In contrast to these prior studies, we did not find significant associations between patient-level socioeconomic factors and risk factor control, with few exceptions. Compared with the costs of modern treatments of ASCVD (surgery, percutaneous interventions), primary prevention is typically quite inexpensive and is far easier to implement across different healthcare systems with lower economic resources. For example, an effective community based initiative to improve BP in rural communities in South Asia cost only about $10 per patient.35 Several studies have shown that simple behavioral interventions for diet and physical activity are associated with significant improvement in risk factor control.36 These efforts are both inexpensive and could translate into substantial cardiovascular risk reduction. Cross-country efforts that incorporate some of these inexpensive and effective strategies that can be implemented across different healthcare systems, economies, and cultures, could therefore have a substantial impact on global health.

Our study had some important potential limitations to discuss. First, while the DISCOVER study included a diverse group of countries from regions across the world, including many countries that have rarely been studied (e.g. Panama, Costa Rica, Bahrain), only 5 countries were below the 2017 World Health Organization GNI/capita threshold for high-income.34 It is not known if our results apply to patients in low income countries where the availability and affordability of essential medicines are markedly limited.38 Second, although the study sites were selected with the intent of enrolling a patient population that was representative of the T2D care in each country,39 potential for selection bias still exists, with sites potentially more focused on quality of care and enrolled patients potentially more compliant with medications and lifestyle recommendations. As such, we expect that our estimates of risk factor control may represent a best-case scenario. Third, we had some patients who were excluded due to missing data, and this could have biased our results. Finally, there are several other country-level and patient-level economic factors we did not have access to that could have been associated with cardiovascular risk factor control. Examining the association of other country-level macro-economic factors, efficiency of healthcare spending, and other healthcare system arrangements with cardiovascular risk factor control remains an area of future work.

In conclusion, we identified substantial gaps in the ability of patients with T2D to achieve optimal risk factor control despite 3 years of follow-up in structured healthcare systems. Neither patient-level nor country-level economic factors were significantly associated with risk factor control. As cardiovascular risk factor control for primary prevention is of critical importance our results highlight the urgent need to incentivize risk factor control to decrease the global burden of ASCVD.

What is already known?

- Patients with type 2 diabetes (T2D), are at an elevated risk of developing atherosclerotic cardiovascular disease (ASCVD).
- Cardiovascular risk factor control for primary prevention, is sub-optimal globally, but patient-level and country-level factors that determine risk factor control have not been established.

What this study adds?

- In a large, multicounty, prospective cohort of patients with T2D, we identified substantial gaps in the ability of patients with T2D to achieve optimal risk factor control despite 3 years of follow-up in structured healthcare systems, across several countries.
- Neither patient-level nor country-level economic factors were significantly associated with risk factor control.

Funding

The DISCOVER study (ClinicalTrials.gov identifiers: NCT02322762, Japan NCT02226822) is funded by AstraZeneca. Drs. Malik and Hejjaji are supported by the National Heart, Lung, And Blood Institute of the National Institutes of Health under Award Number T32HL110837. The final content and the decision to submit was determined solely by the authors.

Individual author disclosures

JK, MBG, LJ, AN, MVS, JV, HW and MK are members of the DISCOVER Scientific Committee and received financial support from AstraZeneca to attend DISCOVER planning and update
meetings. SVA, FT and MK are employees of Saint Luke’s Mid America Heart Institute, which has received research funding from AstraZeneca for participation in DISCOVER. HC and AC are employees of AstraZeneca. JV is a former employee of AstraZeneca. In AstraZeneca for participation in DISCOVER. HC, and AC are employees of Saint Luke’s Mid America Heart Institute, which has received research funding from American Heart Institute, which has received research funding from meetings. SVA, FT and MK are employees of Saint Luke’s Mid America Heart Institute, which has received research funding from

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijhj.2022.07.008.

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