Bridging the Gap: Insights from the AIZANOI Study on Low-Density Lipoprotein-Cholesterol Management in Türkiye

Reaching guideline-recommended low-density lipoprotein (LDL)-cholesterol targets is paramount for cardiovascular prevention due to the central role of LDL-cholesterol in the development of atherosclerotic cardiovascular disease (ASCVD).[1] These guideline-recommended LDL-cholesterol targets are based on extensive clinical evidence linking LDL-cholesterol levels to cardiovascular risk. Achieving these targets significantly reduces the risk of ASCVD events and is the cornerstone of preventive cardiology.

Assessing whether LDL targets are being reached is not only crucial at an individual level but also at a national level. Therefore, registries are extensively used, providing insights into real-world clinical practices.[2] Registries not only provide perspective on a problem within a community but also allow for comparisons with larger reference populations, thus stimulating improvements in the quality and consistency of medical practice. Furthermore, national registries enable comparisons of preventive attitudes across different disciplines, including cardiology, internal medicine, and endocrinology. By revealing existing gaps in knowledge, these registries empower physicians and researchers to develop enhanced detection and prevention strategies.

In their recent work, Şen et al[3] present the AIZANOI study, a multicenter, cross-sectional observational registry conducted across 9 cardiology centers in 4 geographical regions in Türkiye. The AIZANOI study provides valuable insights into real-world dyslipidemia management in cardiology care, particularly regarding adherence to the latest European Society of Cardiology (ESC) dyslipidemia guidelines[1] and the reasons for not reaching LDL-cholesterol targets among patients using statins. The study included 1225 patients who had been on statin therapy for at least 3 months with a diagnosis of dyslipidemia according to the ESC guidelines between August 1 and November 1, 2021. Exclusion criteria were a recent acute coronary syndrome history within 1 month, a glomerular filtration rate <30 mg/dL, and/or triglyceride levels >400 mg/dL. The majority of the study population consisted of very high-risk (90.8%) patients, whereas 4.9% were high risk.

The AIZANOI study revealed that the majority of patients seen in cardiology outpatient clinics are far from the recommended LDL-cholesterol targets. Specifically, less than one-third (26.2%) of the study population had reached the target LDL-cholesterol levels. Among patients at very high risk, 58.4% used guideline-recommended high-intensity statin therapy, while among those at high risk, the percentage was 44.4%. For those with high and very high risk who were using high-intensity statin therapy, only 24.5% and 34.9%, respectively, achieved the LDL-cholesterol goals.

Another important aspect of the AIZANOI study is its detailed comparison between male and female patients. The study revealed significant sex differences in statin therapy and LDL-cholesterol goal attainment. Female patients were less likely to receive high-intensity statin therapy compared to males (61.9% vs. 72.5%, respectively, *P* < .001). Moreover, women were less likely to achieve LDL-cholesterol goals than men among very high-risk patients (20.4% vs. 25.9%,

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respectively). Both men and women showed high compliance with the treatment. However, only 24.7% of female patients and 27.9% of male patients on high-dose statin regimens reached the guideline-recommended target levels. Among very high-risk patients, 54.3% of females and 59.8% of males were on high-intensity statin therapy. For high-risk patients, the rates were 40% for females and 55% for males. Specifically, very high-risk female patients reached LDL-cholesterol target levels at a rate of 20.4%, while their male counterparts achieved this at a rate of 25.9%. In the high-risk category, 27.5% of female patients and 50% of male patients reached LDL-cholesterol target levels.

The results of AIZANOI denote a deep treatment gap consistent with the results of the EPHESUS study.[4] EPHESUS, a country-wide observational study conducted in 40 cardiology centers almost 5 years ago when the 2016 ESC dyslipidemia guidelines were used, showed that only 18% of the EPHESUS population achieved LDL-cholesterol targets, and ezetimibe use was almost lacking in cardiology practice.[5] The consistent underuse of ezetimibe in both EPHESUS and AIZANOI studies is likely due to the reimbursement policy requiring patients to be on statins for at least 6 months with LDL-cholesterol levels higher than 100 mg/dL before ezetimibe can be prescribed in the country.[6] Moreover, only cardiologists, endocrinologists, cardiovascular surgeons, and neurologists may prescribe high-dose statins in Türkiye. Since statin therapy was initiated mostly by cardiologists in both studies, this issue solely could not explain the low ezetimibe use.

It is well known that the reasons for not attaining LDL-cholesterol goals can be broadly categorized into patient-related factors, treatment-related factors, and healthcare system-related factors (Figure 1).[1] The AIZANOI and EPHESUS studies reveal that the major problem in cardiology care in Türkiye is the improper use of low-dose statins and the almost complete lack of combined use of lipid-lowering agents. In the AIZANOI study, adverse effects were responsible for only 3.2% of cases where the

recommended dose of statins was not used, while physician inertia was identified as the major factor. The adverse event factor was similar between men and women (2.5% vs. 3.5%, respectively); however, inertia was higher for women than for men (22.4% vs. 16.5%, respectively; $P = .014$). The EPHESUS study highlighted a 5.6% side effect rate for statin discontinuation, but negative media coverage was the most common cause of statin discontinuation (29.2%), followed by physician recommendations (19.6%) and drug access problems (17.9%).[7]

When both studies are interpreted together, it becomes clear that being far from the LDL-cholesterol goals can mainly be attributed to the inertia of physicians. The 5-year gap between the 2 studies underscores that the issues in achieving LDL goals, which are directly related to the survival of high and very high-risk patients, are still ongoing. Moreover, the change in the LDL-cholesterol attainment rate from 18% in EPHESUS to 26.2% in the AIZANOI population should not be regarded as an improvement in LDL control. First, the 26.2% control rate is still far from the guideline recommendations, and second, the inclusion criteria of both registries are different. Additionally, EPHESUS represents the entire nation, while AIZANOI represents only the central to western part of Türkiye. It is well known that the western part of Türkiye has higher literacy rates, while the eastern part tends to have higher cholesterol levels due to dietary habits, geography, and cold climate. These lifestyle differences might also explain the small difference in results. Of note, the acronyms of these two studies come from two ancient Anatolian cities. AIZANOI is a Phrygian ancient city located in west-central Anatolia. Likewise, Ephesus is an ancient Roman port city located in the West of Anatolia (Figure 2A, 2B).

In conclusion, the AIZANOI study highlights that, even in cardiology practice, Türkiye is still far behind in achieving LDL-cholesterol targets for high and very high-risk patients, underscoring the importance of bridging the gap. One of the most significant findings of this study is that, despite

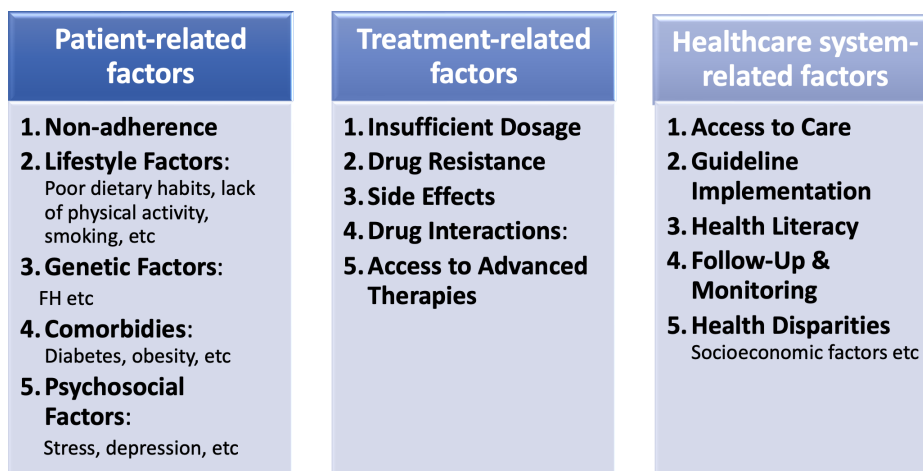| Patient-related factors	Treatment-related factors	Healthcare system-related factors
1. **Non-adherence** 2. **Lifestyle Factors**: Poor dietary habits, lack of physical activity, smoking, etc 3. **Genetic Factors**: FH etc 4. **Comorbidies**: Diabetes, obesity, etc 5. **Psychosocial Factors**: Stress, depression, etc	1. **Insufficient Dosage** 2. **Drug Resistance** 3. **Side Effects** 4. **Drug Interactions**: 5. **Access to Advanced Therapies**	1. **Access to Care** 2. **Guideline Implementation** 3. **Health Literacy** 4. **Follow-Up & Monitoring** 5. **Health Disparities** Socioeconomic factors etc

Figure 1. The reasons for not attaining low-density lipoprotein-cholesterol goals can be categorized into patient-related, treatment-related, and healthcare system-related factors.
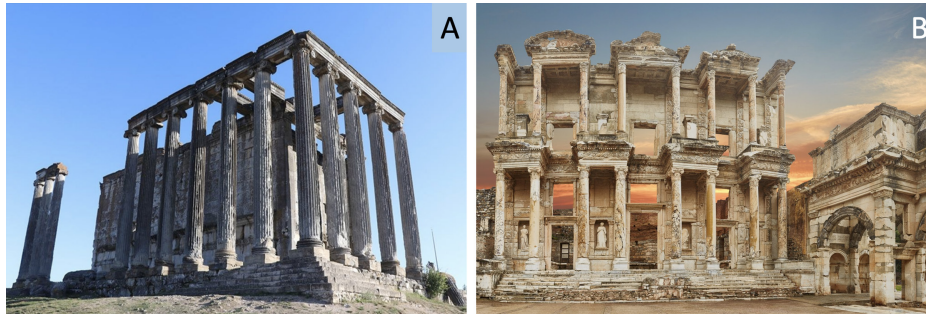
Figure 2. A. AIZANOI is a Phrygian ancient city located in west-central Anatolia. B. EPHESUS is an ancient Roman port city located in the west of Anatolia. Both ancient cities are on UNESCO's World Heritage List.

improved patient adherence to treatment, the main obstacle to reaching LDL-cholesterol targets is physician inertia, which is particularly pronounced in female patients.

Urgent measures are needed in Türkiye to address the issues leading to physician inertia and to enhance the awareness of the cardiovascular risks associated with elevated LDL-cholesterol. Additionally, there is a need to revise reimbursement criteria, particularly for ezetimibe, and to facilitate access to new and effective lipid-lowering agents recommended by guidelines, such as PCSK9 inhibitors, for more effective lipid management.

Given the high cardiovascular risk and the particularly high prevalence of FH in the Turkish population,[6,8] these measures are crucial for improving ASCVD mortality rates. It is imperative to understand the significance of these interventions in reducing the overall burden of ASCVD in Türkiye.

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