

ORIGINAL ARTICLE

Rationale, design, and methodology of the EPIC (Epidemiology of Polypharmacy and Potential Drug-Drug Interactions in Elderly Cardiac Outpatients) study

EPIC (Yaşlı, Ayaktan Kardiyak Hastalarda Polifarmasi ve Potansiyel İlaç-İlaç Etkileşimlerinin Epidemiyolojisi) çalışmasının temel, tasarım ve metodolojisi

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ABSTRACT

Objective: The aim of this study is to assess the prevalence of polypharmacy, inappropriate drug use, and drug-drug interactions (DDIs) in elderly patients presenting at outpatient cardiology clinics in Turkey.

Methods: The EPIC (Epidemiology of Polypharmacy and Potential Drug-Drug Interactions in Elderly Cardiac Outpatients) study will be an observational, real-world, multicenter study conducted to evaluate DDIs and polypharmacy in elderly cardiac outpatients. All consecutive patients (aged ≥65 years) admitted to outpatient cardiology clinics between July 30, 2018 and July 30, 2019 who provide written, informed consent will be enrolled. A total of approximately 5000 patients are to be enrolled in this non-interventional study. All of the data will be collected at one point in time and current clinical practice will be evaluated (ClinicalTrials.gov NCT03370523).

Results: Patient demographics, comorbid disease characteristics, laboratory test results, and details of medication use will be collected using self-reports and medical records. The severity of comorbid disease will be recorded and scored according to Charlson Comorbidity Index (CCI) and patients will be divided into 3 groups: mild, those with a CCI score of 1–2; moderate, those with a CCI score of 3–4; and severe, those with a CCI score of ≥5. Polypharmacy will be defined as the use of 5 or more medications at one time. DDIs will be determined using the Lexicomp Online drug interaction screening tool and potentially inappropriate medications will be defined based on the 2015 update of the Beers Criteria for Potentially Inappropriate Medication Use in Older Adults. Severe drug interactions will be defined as those in category D or X.

Conclusion: EPIC will be the first large-scale study in Turkey to evaluate polypharmacy, potentially inappropriate medications, and DDIs in elderly cardiac outpatients in a real-world clinical setting.

ÖZET

Amaç: Türkiye'deki kardiyoloji polikliniklerine başvuran yaşlı hastalarda polifarmasi prevalansını, uygunsuz ilaç kullanımını ve ilaç-ilaç etkileşimlerini (İİE) değerlendirmek.

Yöntemler: EPIC (Epidemiology of Polypharmacy and Potential Drug-Drug Interactions in Elderly Cardiac Outpatients) çalışması kardiyoloji polikliniklerine başvuran yaşlı hastalarda polifarmasi ve İİE'nin değerlendirileceği, gerçek yaşam verilerini aktaran, çok merkezli ve gözlemsel bir çalışma olarak tasarlandı. Çalışmaya; 30 Temmuz 2018 ve 30 Temmuz 2019 tarihleri arasında farklı kardiyoloji polikliniklerine başvuran, aydınlatılmış onam formunu imzalayan, 65 yaş ve üzeri, kadın ve erkek, ardışık 5000 hastanın dahil edilmesi planlandı. Hastalarla ilgili tüm verilerin tek bir ziyarette alınması ve verilerin değerlendirilmesi planlandı (ClinicalTrials.gov numarası NCT03370523).

Bulgular: Hastalara ait demografik veriler, komorbid hastalık durumları, laboratuvar test sonuçları ve ilaç bilgileri hasta beyanları ve medikal kayıtlar yoluyla toplanacaktır. Komorbid hastalıklar kaydedilecek ve komorbid hastalıkların ciddiyeti Charlson komorbidite indeksi'ne (CKİ) göre hastalar 3 gruba ayrılacaktır: CKİ skoru 1–2 olanlar hafif, CKİ skoru 3–4 olanlar orta, CKİ skoru ≥5 olanlar ciddi. Polifarmasi aynı hastanın bir keredede 5 ve üzeri ilaç kullanması olarak tanımlanacaktır. İİE Lexicomp® çevrimiçi ilaç etkileşimi tarama aracı ile kontrol edilecek, potansiyel uygunsuz ilaç kullanımını 2015 Beers kriterlerine göre tanımlanacaktır. D ve X kategorisindeki etkileşimler ciddi ilaç etkileşimi olarak sınıflandırılacaktır.

Sonuç: EPIC çalışması kardiyoloji polikliniklerine başvuran yaşlı hastalarda polifarmasi, İİE ve potansiyel uygunsuz ilaç kullanımı konularında gerçek yaşam verilerini ayrıntılı olarak aktaran ilk büyük çaplı çalışma olacaktır.

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Old age, defined as the “period of life when impairment of mental and physical functions becomes increasingly manifest by comparison with previous periods of life” by the World Health Organization Psychogeriatrics Science Group, is generally accepted as beginning at 65 years of age.^[1] While the elderly population aged 65 years and over in Turkey was 5,891,694 in 2013 according to Turkish Statistical Institute (TSI) data, it increased by 17% in the last 5 years, rising to 6,895,385 individuals in 2017 data. According to population projections, the elderly proportion of the population in Turkey is expected to be 10.2% in 2023, 12.9% in 2030, 16.3% in 2040, 22.6% in 2060, and 25.6% in 2080. TSI cause of death data also reveal that in 2016, 45.6% of the elderly died as a result of diseases of the circulatory system, followed by neoplastic diseases at 16.3%, and respiratory system diseases at 13.9%.^[2]

As a result of the growing proportion of the elderly in the general population, increases in the incidence of multiple chronic diseases, multiple drug prescriptions, drug-drug interactions (DDIs), and polypharmacy (defined as the regular use of 5 or more drugs) are unavoidable. The concomitant use of multiple medications can contribute to undesirable health outcomes among older patients, such as an increase in adverse reactions and DDIs, lower adherence to drug therapy, decreased functional capacity, and cognitive decline.^[3] In addition, polypharmacy can result in a greater demand for care, an increase in the number of hospital admissions, and higher costs for the health system.^[4]

In a recent study, Abunahlah et al.^[5] examined drug-related problems in a Turkish hospital, as well as the causes. This small, cross-sectional study included a total of 100 patients. The research revealed that at least 1 potential drug-related problem was seen in 80% of the patients, and a total of 163 potential drug-related problems were identified. The most common causes of drug-related problems were errors in drug selection, dose selection, and medication procedures. Patients with renal impairment, inflammation, polypharmacy, or an extended hospital stay had a much greater chance of developing a drug-related problem. Although the incidence and consequences of polypharmacy and DDIs in elderly patients have already been documented in Western countries,^[6-8] few data are available in developing countries. Therefore, the current study was designed to determine the preva-

lence of polypharmacy, DDIs, and potentially inappropriate drug use among elderly patients admitted to cardiology outpatient clinics in Turkey.

Abbreviations:

CCI	Charlson comorbidity index
DDI	Drug-drug interaction
EPIC	Epidemiology of Polypharmacy and Potential Drug-Drug Interactions in Elderly Cardiac Outpatients
TSI	Turkish Statistical Institute

METHODS

Participants and setting The EPIC study (Epidemiology of Polypharmacy and Potential Drug-Drug Interactions in Elderly Cardiac Outpatients) is designed to be a multicenter, non-interventional (observational), cross-sectional, descriptive study evaluating polypharmacy and DDIs in Turkey. Only patients who were followed up in cardiology outpatient clinics in the period between July 30, 2018 and July 30, 2019 will be enrolled. A total of 5000 elderly individuals from 12 provinces in different regions of the country are to be included. The geographic distribution of hospitals across the country and the overall profile of the participating cardiology institutions are to be representative of the national profile of cardiovascular care in Turkey. Data will be collected from a total of 25 cardiologists. The study will not stipulate any diagnostic or treatment procedures. This research was approved by the institutional review board or local ethics committee and the study has been registered with ClinicalTrials.gov (NCT03370523).

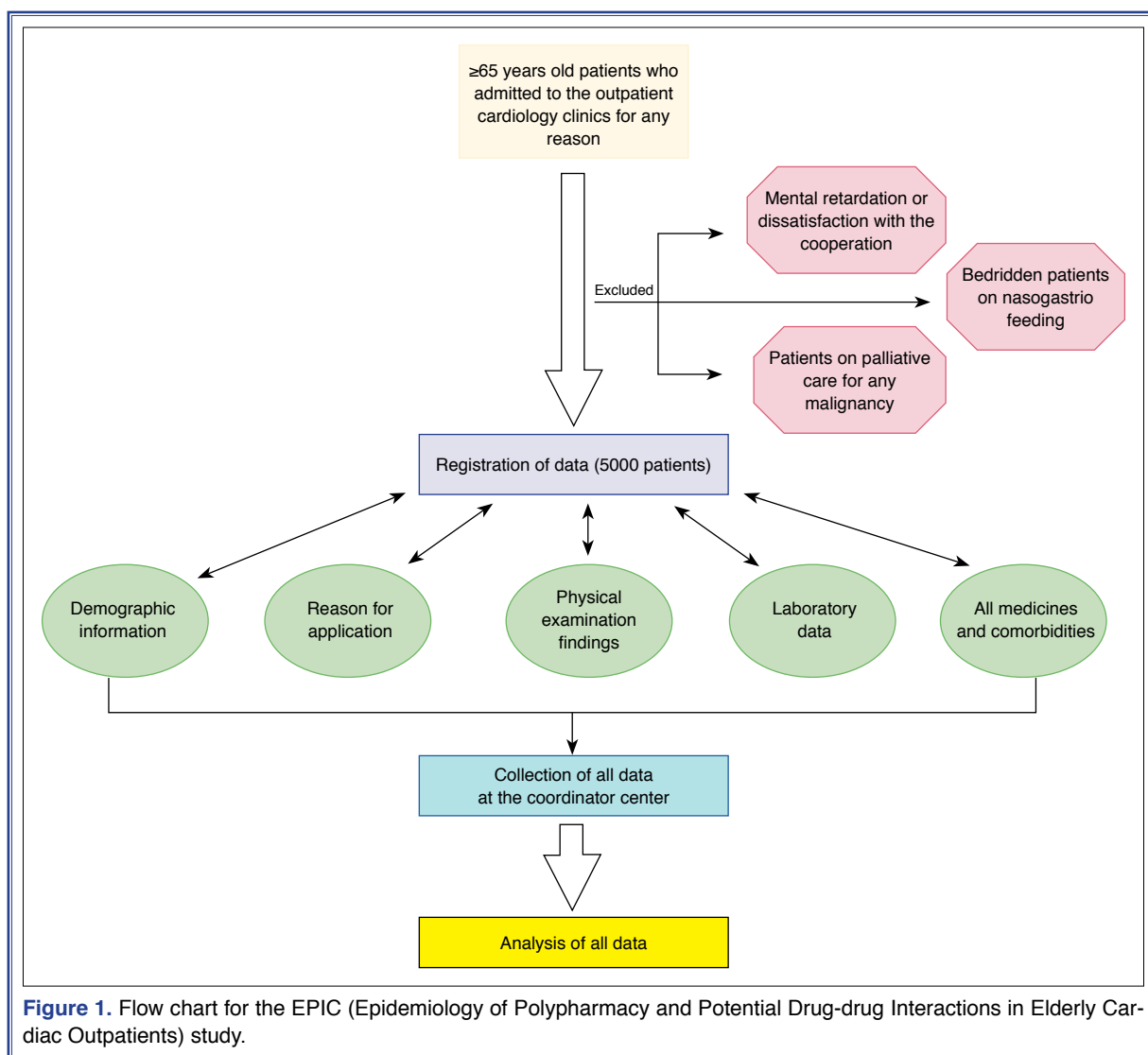
RESULTS

Figure 1 illustrates the work flow. Enrollment will occur during a routine visit; A physician will conduct a face-to-face interview with elderly patients who are admitted to cardiac outpatient clinics in each participating province. All consecutive patients eligible on the basis of the criteria described below will be included in the study.

Inclusion criteria

To qualify for enrollment in the study, outpatients must fulfill the following eligibility criteria:

1. Aged 65 years or older on May 30, 2018 and admitted to a cardiology outpatient clinic regardless of complaints, comorbidities, or living setting,
2. Willingness to participate and provide written, informed consent.



Exclusion criteria

1. Patients aged less than 65 years,
2. Presence of mental retardation or unwillingness to participate,
3. Palliative care for any malignancy or bedridden status on nasogastric or percutaneous endoscopic gastrostomy feeding.

Measurements

Table 1 provides a summary of the items on the EPIC survey questionnaire.

Information on the following variables will be collected for each patient; age, sex, marital status, level of education, smoking history, alcohol use, place of residence (rural or urban), body mass index, retirement sta-

tus, systolic and diastolic blood pressure, heart rate and rhythm, responsibility for the preparation and administration of drugs, all chronic medical conditions and number of diseases, number of prescribers, signs and symptoms at presentation, and laboratory test results. The laboratory parameters to be collected are fasting plasma glucose, cholesterol parameters, triglycerides, creatinine, aspartate aminotransferase, alanine aminotransferase, uric acid, hemoglobin, platelet counts, sodium, potassium, and calcium levels.

Definitions

Medication count: All prescription or non-prescription medications taken by the patient will be counted as a medication. Tablets and capsules will be counted as pills, while other medications will be counted as non-pills. Drugs without a systemic action (e.g., arti-

Table 1. Summary of the EPIC survey questionnaire

Number of patients	5000	Comorbidities
Study type	* Multicenter, cross-sectional, observational	* Atrial fibrillation * Hypertension * Diabetes mellitus * Heart failure with reduced ejection fraction * Renal failure * Obstructive sleep apnea syndrome * Hyperlipidemia * History of myocardial infarction * Coronary artery disease * Cardiac pacemaker * Peripheral artery disease * Cerebrovascular disease * Chronic obstructive pulmonary disease * Liver disease * Depression * Solid tumor * Lymphoma/leukemia * Prosthetic heart valve * Hemiplegia * Rheumatic disease * Connective tissue disease * Acquired immune deficiency syndrome * Dementia * Peptic ulcer * Thyroid dysfunction * Anemia * Osteoporosis
Patient population	* Patients 65 years and over who presented to the outpatient cardiology clinics	
Demographic information	* Gender * Age * Body mass index * Smoking history * Place of residence * Level of education * Alcohol use	
Reason for application	* Breathlessness * Palpitations * Fatigue, tiredness * Syncope * Dizziness * Chest pain * Hypertension * Hypotension * Routine control * Prescription * Drug side effect	
Physical examination findings	* Blood pressure * Heart rate * Cardiac murmur * Peripheral edema * ECG abnormality	
Laboratory data	* Laboratory data * Fasting blood glucose * Blood urea nitrogen * Serum creatinine * Serum sodium * Serum potassium * Serum calcium * Serum uric acid * Hemoglobin * Platelet * Total cholesterol * LDL cholesterol * HDL cholesterol * Triglycerid	
Medication	* All medicines used by patients will be recorded.	

ECG: Electrocardiogram; LDL: Low-density lipoprotein; HDL: High-density lipoprotein.

ficial tear fluid) or drugs not taken at regular intervals during the 2 weeks before admission will be excluded from the analysis.

Polypharmacy: Polypharmacy will be defined as the concurrent use of ≥ 5 medications daily, including over-the-counter drugs, for at least 3 months.

Drugs without an indication: Drugs with no proven or with a controversial benefit in long-term therapy, or those used without medical requirement are defined as drugs without an indication, such as ginkgo biloba and peripheral vasodilators like pentoxifylline for the treatment of dementia, β -adrenergic agents to elevate blood pressure, or allopurinol in patients without a history of gout or excessively elevated uric acid, and all medical products not used with the appropriate indication.

Health status: The individual health status of the patients and the severity of comorbid diseases will be recorded and scored according to the Charlson Comorbidity Index (CCI), a score based on 19 chronic diseases. Patients will be divided into 3 groups: mild, a CCI score of 1–2; moderate, a CCI score of 3–4; and severe, a CCI scores ≥ 5 .

Drug-drug interactions: Drug interactions will be assessed using the Lexicomp Online drug interaction screening tool (Wolters Kluwer Clinical Drug Information, Inc., Hudson, OH, USA). This system categorizes the interaction into 5 subgroups and provides a recommendation for a clinical approach for each category (A, B, C, D, and X). The recommendation for category D is “consider therapy modification” and it is “avoid combination” for category X. The presence of either a category D or X interaction will be defined as a severe DDI.

Potentially inappropriate medications: When the risk of adverse events due to treatment with a particular medication outweighs the clinical benefit, it may be a potentially inappropriate medication. The term will be broadened to “inappropriate medications” in the EPIC study and based on the 2015 update of the Beers Criteria for Potentially Inappropriate Medication Use in Older Adults.

Statistical analyses

Summary statistics will be provided as percentages or as mean with SD. Baseline continuous variables will be presented as mean \pm SD or median and interquar-

tile range, according to the distribution of the data, and categorical data will be presented as counts and percentages. Categorical variables will be compared using a chi-square test and a t-test or the Mann-Whitney U test will be used for the continuous variables, as appropriate. Univariate and multiple regression analysis will be used to calculate odds ratios and 95% confidence intervals. Analyses will be performed using IBM SPSS Statistics for Windows, Version 24.0 (IBM Corp., Armonk, NY, USA) or a more recent version.

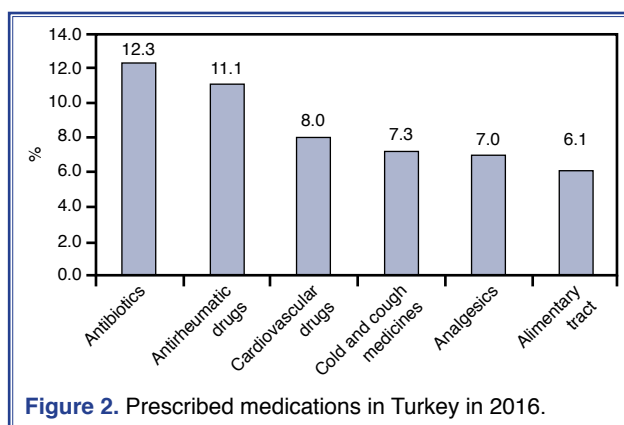
DISCUSSION

There has been a growing increase in the number of elderly patients worldwide. Since elderly patients are more fragile, the approach of clinicians to this patient population requires specialization.^[9] Polypharmacy is common in elderly outpatients and has been identified as a major risk factor for DDIs, which are an important cause of adverse drug reactions.^[10] Elderly patients tend to have more complicated chronic conditions, may respond differently to medical therapies, or experience more severe adverse reactions due to differences in pharmacokinetic and pharmacodynamic characteristics, compared with younger patients. Elderly patients may also visit multiple physicians and use multiple pharmacies, which may lead to an increased risk of medication-related problems.^[11] The EPIC study aims to: (1) determine the prevalence of polypharmacy, DDIs, and inappropriate medication use in elderly patients admitted to cardiology outpatient clinics; (2) demonstrate the current clinical background of polypharmacy patients; (3) analyze the predictors of polypharmacy patients and their comorbidities; and (4) investigate the predictive accuracy of the CCI on polypharmacy and incidence of inappropriate medication use in a large, multicenter study.

Studies have revealed that the rapidly aging global population and the increased number of medications used over the last 20 years have led to an increased risk of polypharmacy, adverse drug reactions, and DDIs. In a recent study, about 1.7 million older Swedish adults were followed for up to 3 years (from 2010 to 2013) through various health registers.^[12] In this study, Morin et al.^[12] reported that the prevalence of polypharmacy (≥ 5 drugs) was 44.0% and the prevalence of excessive polypharmacy (≥ 10 drugs) was 11.7%. They found that greater age, more chronic diseases, and multi-dose dispensing led to a more frequent exposure to

polypharmacy. In another study, an analysis of potential DDIs was performed using health claims data for prescription drugs from a nationwide database.^[13] The study population included 1,179,803 outpatients who received 15,811,979 prescriptions and revealed that 1 in 10 individuals in the total Slovenian population was exposed to clinically relevant potential DDIs yearly. A large number of medications and older age were associated with higher odds of clinically relevant potential DDIs.^[13] Suzuki et al.^[14] analyzed the records of all prescriptions issued to patients aged ≥ 65 years at 585 dispensing pharmacies in a cross-sectional study across Japan. They found that the proportion of polypharmacy/hyperpolypharmacy, defined as having more than 5/10 regular medications, increased with age (65–74 age group: 27.2%/5.1%; 75–84 age group: 36.0%/9.6%; and >85 years group: 47.3%/15.6%).

Potentially inappropriate medications are drugs that are defined as inappropriate when the risks outweigh the benefits, especially when there are safer alternatives.^[15] Several tools have been developed to identify potentially inappropriate medications in the elderly; the most known and frequently used is the Beers List, which was updated by the American Geriatrics Society in 2015.^[15] A careful search of the available literature revealed few studies on potentially inappropriate medications in patients with cardiovascular diseases using the current Beers criteria. Moreover, to the best of our knowledge, there are no studies in Turkey evaluating potentially inappropriate medications using the current Beers criteria in any specialty of medicine. The EPIC study will be the first to determine the frequency and factors associated with potentially inappropriate medications in older patients admitted to cardiology outpatient clinics in Turkey, and will use the updated 2015 Beers criteria.



Cardiovascular medications are one of the most commonly prescribed drugs in Turkey. According to 2016 data, they represented 8% of all prescriptions, or the third most common group (Fig. 2).^[16] Various studies have suggested that cardiovascular patients have more DDIs than patients with other diseases.^[17,18] Possible reasons for a higher DDI rate in cardiovascular disease patients may include older age, multiple-drug regimen, and the pharmacokinetic or pharmacodynamic nature of drugs used in cardiology. A study reported by Cruciol-Souza and Thompson^[19] found that the overall frequency of DDIs was 49.7% in cardiology patients. Although drug interactions have been reported to be common among cardiology patients, there is no published report of the prevalence of such interactions among Turkish cardiac patients. Polypharmacy, DDIs, and inappropriate medications have been studied in numerous observational and interventional studies in the European countries and the USA, but these data are limited in our country. The only multicenter study in Turkey was performed 10 years ago.^[20] A total of 1430 elderly individuals from 12 provinces in different geographic regions of Turkey were included in a cross-sectional study conducted between January 2007 and January 2008. A face-to-face interview was conducted by the physicians with elderly patients at outpatient clinics of medical schools and departments of physical medicine and rehabilitation in each province. The mean number of drugs used was 2.69 for females and 2.14 for males ($p < 0.001$). The mean number of drugs used by participants aged between 65 and 69 years was 2.27, while it was 2.71 for those aged 70 to 74, and 2.66 for those 75 years and older ($p = 0.001$). The results of this study indicated that females with chronic medical conditions tended to use more drugs compared with their male counterparts. In another unicenter study, 667 patients aged ≥ 65 years admitted to the outpatient clinic of a university hospital were retrospectively evaluated for potentially inappropriate medication using the Beers 2012 criteria and the Screening Tool of Older Persons' Prescriptions (STOPP) version 2.^[21] This study results indicated that the STOPP rate of detecting potentially inappropriate medication use was higher than that of the Beers 2012 criteria (39.1% vs 33.3%, respectively; $p < 0.001$). Antipsychotics, over-the counter vitamin/supplements, aspirin, selective-serotonin-reuptake-inhibitors, and anticholinergics were the leading drug classes for a potentially inappropriate medica-

tion. The extent of polypharmacy was the most important variable related to potentially inappropriate medication use, along with the multiple comorbidities. A greater level of functionality was inversely associated with potentially inappropriate medications.^[21]

DDIs are usually defined as 2 or more drugs interacting in such a manner that the effectiveness or toxicity of 1 or more drugs is altered.^[22] The potential for drug interaction is higher with cardiac drugs.^[23] However, there are no studies reporting the actual incidence of DDIs in the Turkish setting. The EPIC study is designed to assess the incidence and pattern of DDIs in cardiac outpatients and provide an assessment of reaction characteristics and causality. Drug interactions will be assessed using the Lexicomp Online drug interaction screening tool. This system categorizes the interaction into 5 subgroups and provides a recommendation for a clinical approach for each category (A, B, C, D, and X). The recommendation for category D is “consider therapy modification” and it is “avoid combination” for category X.

Comorbidities may directly affect the prognosis of the disease of interest or indirectly influence the choice of treatment. The CCI, introduced in 1987 to predict the 1-year mortality in a cohort of young patients, is the most widely used comorbidity index.^[24] This index contains 19 conditions, including diabetes with diabetic complications, congestive heart failure, chronic pulmonary disease, peripheral vascular disease, mild and severe liver disease, hemiplegia, renal disease, leukemia, lymphoma, metastatic tumor, and AIDS, each of which is weighted according to the potential influence on mortality (Table 2). The original CCI has been adapted and verified as applicable and valid for predicting the outcome and risk of death from many comorbid diseases.^[25] A few studies have also shown that higher CCI scores were associated with the highest frequencies of potential inappropriate drug use.^[26] Therefore, an aim of the EPIC study is to investigate the predictive accuracy of the CCI on polypharmacy and the incidence of inappropriate medications.

Limitations

Observational studies such as the EPIC study have been proposed as alternative means of testing intervention effectiveness in older populations with multifaceted problems. The EPIC study will assess outcomes in regular clinical practice, thereby reflecting

Table 2. Charlson Comorbidity Index Scoring System

Score*	Condition
1	Myocardial infarction history Congestive heart failure Peripheral vascular disease Cerebrovascular disease Chronic pulmonary disease Dementia Connective tissue disorder Peptic ulcer disease Mild liver disease Diabetes without end-organ damage
2	Hemiplegia Diabetes with end-organ damage Moderate or severe renal disease Tumor without metastases Any leukemia or lymphoma
3	Moderate or severe liver disease
6	Metastatic solid tumor Acquired immune deficiency syndrome

*In addition, for each decade >40 years of age, a score of 1 was added to the comorbidity score.

real adherence to treatment/intervention. However, our study will not be able to differentiate between cause and effect or the sequence of events. Such research is useful for identifying associations that can then be more rigorously studied using a cohort study or randomized controlled study. The EPIC study will not be able to observe the course of disease, and information regarding prognosis data will be limited. In addition, the study is limited in that the coverage is restricted to a single specialty.

Conclusions

In summary, elderly patients, especially those with cardiovascular disorders, are at higher risk for DDIs because of the types and number of drugs they use. While drug interactions are reported to be common, there is no published report of the prevalence of such interactions among Turkish cardiac patients. The EPIC study will be the largest study among Turkish patients to evaluate the frequency of polypharmacy and to assess the relationship between polypharmacy and potential adverse outcomes within a sample of elderly population admitted to cardiology outpatient clinics. The findings of this study will provide important real-

world evidence, as well as potentially provide a better understanding of the burden of polypharmacy.

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