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RESEARCH

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Real-world research on beta-blocker usage trends in China and safety exploration based on the FDA Adverse Event Reporting System (FAERS)

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Abstract

Background Beta-blockers are widely used, with continuously updated clinical recommendations. However, their application faces challenges in personalized treatment and safety. The study aimed to investigate the frequency and patterns of prescribing beta-blockers in China and to explore potential adverse event risk signals associated with beta-blockers, providing reference for rational medication use in clinical settings.

Methods Prescription data for beta-blockers from January 2018 to June 2023 were extracted through the Hospital Prescription Analysis Collaborative Project in China to analyze clinical usage trends. While adverse drug reaction reports for beta-blockers were obtained from the FDA Adverse Event Reporting System (FAERS) database. The classification and standardization of adverse drug event (ADE) reports were based on the preferred terms (PT) and corresponding system organ classes (SOC) from the Medical Dictionary for Regulatory Activities (MedDRA). Signal detection utilized a proportion imbalance method.

Results In clinical practice, metoprolol dominated beta-blocker prescriptions in China, accounting for 62.2%. Beta-blockers were primarily prescribed to the elderly (65.7%) and male patients (57.0%). However, off-label use of beta-blockers was relatively widespread. For instance, sotalol was prescribed for hypertension at 18.25%, while esmolol was used for angina and heart failure at rates of 12.94% and 14.98%, respectively. In addition, we identified newly discovered adverse reactions associated with beta-blockers, such as BRASH syndrome (metoprolol: $n = 186$, ROR = 391.285; carvedilol: $n = 72$, ROR = 256.459), acute kidney injury (bisoprolol: $n = 247$, ROR = 5.641), premature baby (labetalol: $n = 110$, ROR = 91.385), and sleep disorder (propranolol: $n = 254$, ROR = 10.98).

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Conclusions Metoprolol led the beta-blocker market in China. Attention was warranted regarding the newly discovered adverse reactions, such as the risk of acute kidney injury with bisoprolol and the potential for BRASH syndrome with metoprolol and carvedilol.

Keywords Beta-blockers, Real-world research, Safety, Metoprolol, Adverse drug event

Introduction

Since their introduction in the 1960s, beta-blockers have become essential medications in clinical practice. Over the years, a growing variety of beta-blockers have been developed, offering broader options and treatment possibilities in the medical field. These drugs play a vital role in managing cardiovascular conditions such as angina, hypertension, and heart failure, and they have also demonstrated effectiveness in treating migraines and essential tremors.

Beta-blockers exhibit significant heterogeneity, primarily due to their cardiac selectivity, lipophilicity, and intrinsic sympathomimetic activity. These characteristics not only influence their mechanisms of action but also determine their therapeutic indications. Consequently, challenges in selecting the appropriate beta-blocker have emerged as a significant issue, hindering clinicians from effectively utilizing these medications.

Over the past decade, recommendations regarding the use of beta-blockers have gradually evolved. For instance, in the case of hypertension—the most common indication—some guidelines [1, 2] have no longer positioned beta-blockers as the first-line initial treatment, instead favoring calcium channel blockers (CCBs), angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), and diuretics. Beta-blockers were generally reserved for patients with specific complications or conditions, such as heart failure, angina, myocardial infarction, atrial fibrillation, or for young women who were pregnant or planning to become pregnant. The 2023 ESH guidelines [3] once again included beta-blockers among the five major classes of anti-hypertensive drugs for initial treatment, a decision that might have been somewhat controversial. On the one hand, beta-blockers demonstrated clear efficacy in lowering blood pressure, and concerns regarding their potential to cause depression or erectile dysfunction seemed to be overstated. In fact, for patients with chronic obstructive pulmonary disease (COPD) or peripheral artery disease, whose treatment options were limited, the use of beta-blockers might have provided significant therapeutic benefits [4]. However, some studies suggested that beta-blockers were significantly less effective than other anti-hypertensive medications in preventing stroke and cardiovascular death, and upgrading the use of beta-blockers could potentially have led to widespread harm due to poorer protection against strokes [5]. Due to the widespread application of beta-blockers across various fields and the continuous updates in recommendations in recent years, coupled with the diversity and heterogeneity of beta-blockers themselves, clinical practice might have faced challenges in selection and lack of standardization.

Beta-blockers, commonly used to manage cardiovascular conditions such as hypertension, heart failure, and arrhythmias, play a crucial role in addressing the growing burden of cardiovascular diseases (CVDs) in China, which is the leading cause of death in the country [6]. By analyzing real-world usage trends, this study offers valuable insights into prescription patterns, patient population characteristics, and regional disparities in access to beta-blockers. These findings could assist healthcare policymakers in optimizing cardiovascular treatment strategies, thereby improving patient outcomes and reducing the economic burden of CVDs, which pose significant challenges to both individual households and the national healthcare system [7]. Moreover, the utilization of the FDA adverse event reporting system (FAERS) database for safety exploration allows for a comprehensive assessment of adverse drug events (ADEs), a key factor in ensuring patient safety and informing regulatory decisions. Identifying potential safety risks can help prevent harmful side effects, reduce healthcare costs associated with ADEs, and bolster public confidence in medical treatments [8]. Ultimately, this study has the potential to enhance the quality of care, promote cost-effective healthcare, and improve overall population well-being in China. The study aimed to explore the clinical usage of beta-blockers in China based on real-world data from the Hospital Prescription Analysis Collaborative Project and to conduct a preliminary assessment of the rationality of beta-blocker prescriptions. Additionally, we sought to leverage the FAERS database to uncover potential adverse event risk signals associated with beta-blockers, providing evidence for rational drug use in clinical practice.

Methods

Data analysis of the hospital prescription analysis collaborative project

Study sample

This section extracted prescription data for beta-blockers from the "Hospital Prescription Analysis Collaborative Project" conducted by the Pharmacy Professional Committee of the Chinese Pharmaceutical Association, covering the period from January 2018 to June 2023. The data included samples from hospitals in nine regions: Beijing, Shanghai, Guangzhou, Hangzhou, Chengdu, Tianjin,

Zhengzhou, Shenyang, and Harbin. Every quarter, prescriptions from 10 randomly selected working days were collected from both outpatient and inpatient departments. We defined the prescription selection criteria based on the target drug class of beta-blockers, ensuring that only those prescriptions explicitly containing beta-blockers were included. These drugs comprise metoprolol, bisoprolol, esmolol, arotinolol, carvedilol, carteolol, labetalol, sotalol, propranolol, timolol, atenolol, betaxolol, and bevantolol. Inclusion criteria: ①The prescription includes the target beta-blocker drugs. ②The prescription date falls within the study's time frame. ③The prescription originates from both outpatient and inpatient departments. Exclusion criteria: ①Duplicate prescriptions. ②Prescriptions that lack age information or diagnostic information (Fig. 1).

Study design

In this study, we performed a descriptive analysis of beta-blocker prescriptions, including a statistical evaluation of the prescription numbers for various beta-blockers. We also organized relevant patient information, such as gender, age, department, region, and hospitalization status, to enhance our sample data. The prescription included the original diagnosis, which was coded and classified according to the International Classification of Diseases,

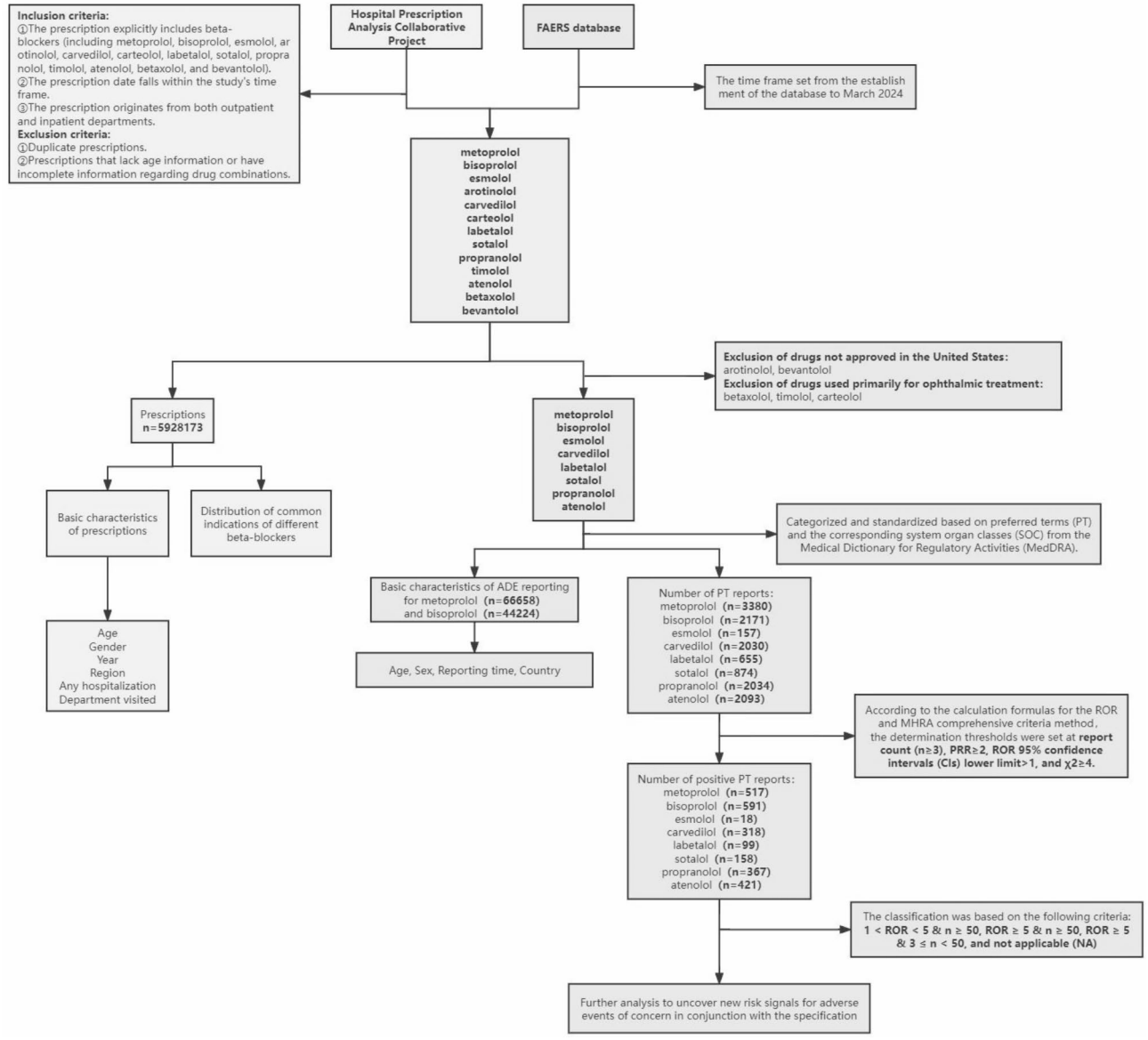

Fig. 1 The flowchart depicts the study design, including the selection process for data extraction and analysis. It outlines the key steps taken in the study, such as the identification of eligible prescriptions and the criteria for inclusion and exclusion. Additionally, it describes the overall methodology used for data collection and analysis from the Hospital Prescription Analysis Collaborative Project and the FAERS database

10th Edition (ICD-10). Based on the original diagnoses in the prescriptions, we calculated the usage proportions of various beta-blockers for common indications (such as hypertension, heart failure, and angina pectoris). We compared these proportions to the approved indications outlined in the drug labeling and the recommendations in clinical guidelines, which enabled us to assess the rationality of medication use across different types of beta-blockers. The basic characteristics of different beta-blocker prescriptions were described using the number of prescriptions and percentages, while the usage of different beta-blockers and the original diagnoses for their prescription were described using proportions.

Data analysis of the FAERS database

Data source

The FAERS database provides a wealth of medical information, including drug usage, patient information regarding ADEs, and reporter details, which helps better understand drug safety and inform timely policies and regulatory measures [9]. This study collected adverse event information related to beta-blockers from the FAERS database and conducted data analysis to perform signal detection for ADEs of beta-blockers, further analyzing their safety to provide a reference for the clinically safe use of these drugs.

Using the OpenVigil 2.1 website (http://openvigil.sourceforge.net), we conducted searches for the target drugs metoprolol, bisoprolol, esmolol, carvedilol, labetalol, sotalol, propranolol, and atenolol, designating them as primary suspects in relation to reported adverse events. The time frame for our searches was set from the establishment of the database to March 2024. We excluded the drugs arotinolol and bevantolol, which were not approved for marketing in the United States, as well as betaxolol, timolol, and carteolol, which were primarily used for ophthalmic treatments (Fig. 1).

Data processing

We extracted data on the most frequently used metoprolol and bisoprolol from ADE reports, including patient age, gender, clinical outcomes, reporting country, and reporting date, and conducted statistical analysis to summarize the basic information of ADE reports. ADE reports were categorized and standardized based on preferred terms (PT) and the corresponding system organ classes (SOC) from the Medical Dictionary for Regulatory Activities (MedDRA), which was a standardized medical vocabulary that helped streamline the recording and reporting of ADE data on a global scale [10].

This study utilized the proportional imbalance method for signal detection, employing the reporting odds ratio (ROR) method and the comprehensive criteria method from the Medicines and Healthcare Products Regulatory Agency (MHRA) to analyze ADE report data. The fourfold table of disproportionality measurement is provided in Table 1. The ROR method, developed by the Lareb laboratory at the Dutch Pharmacovigilance Centre, is recognized for its reduced bias and enhanced sensitivity. The MHRA method, which builds upon the PRR method by integrating PRR values, absolute report counts, and chi-square statistics while ensuring a minimum case combination, is noted for its high sensitivity and consistent results [11]. According to the calculation formulas for the ROR and MHRA comprehensive criteria method (Table 2), the determination thresholds were set at report count ($n \geq 3$), PRR ≥ 2, ROR 95% confidence intervals (CIs) lower limit > 1, and $\chi^2 \geq 4$. The stronger the signal value, the greater the statistical association between the target drug and the corresponding ADE. To categorize the eight beta-blockers based on their ROR and the number of reports into the top 10 PTs, they were classified into three categories: non-selective beta-blockers, selective beta1-blockers, and alpha-beta blockers. The same PTs from different drugs within the same category were merged. The classification was based on the following criteria: $1 < ROR < 5$ & $n \geq 50$, $ROR \geq 5$ & $n \geq 50$, $ROR \geq 5$ & $3 \leq n < 50$, and not applicable (NA).

Table 1 The fourfold table of disproportionality measurement

Drug	Target Adverse Event Report	Other Adverse Event Reports	Total
Target Drug	a	b	a + b
Other Drugs	c	d	c + d
Total	a + c	b + d	a + b + c + d

Note a, number of reports containing both the target drug and the target adverse drug event; b, number of reports containing other adverse drug events of the target drug; c, number of reports containing the target adverse drug event of other drugs; d, number of reports containing other drugs and other adverse drug events

Table 2 Formulas and criteria of ROR and MHRA methods

Methods	Formula	Signal decision threshold
ROR	$ROR = ad/bc$ $95\%CI = e^{\ln(ROR) \pm 1.96(1/a+1/b+1/c+1/d)\text{^}0.5}$	95% CI lower limit > 1, $n \geq 3$
MHRA	$PRR = (a/(a+b))/(c/(c+d))$ $\chi^2 = (ad-bc)^2 (a+b+c+d)/[(a+b)(c+d)(a+c)(b+d)]$	$PRR \geq 2$, $\chi^2 \geq 4$, $n \geq 3$

Note n, the number of reports

Results

Basic prescription information

This study included a total of 5,928,173 prescriptions, with the basic information summarized in Table 3. Outpatient prescriptions accounted for 53.7%, while inpatient prescriptions accounted for 46.3%. Patients were grouped by age, and the proportion of those using beta-blockers increased with age. Among patients over 60 years old, the usage of beta-blockers was the highest, reaching 65.7%,

Table 3 Demographic characteristics of prescriptions

Characteristic	Prescriptions(N = 5,928,173)	Proportion(%)
Age		
0–17	40,784	0.7
18–44	626,509	10.6
45–59	1,361,917	23.0
>60	3,898,963	65.7
Gender		
Male	3,380,247	57.0
Female	2,547,926	43.0
Year		
2018	1,148,920	19.4
2019	1,195,253	20.2
2020	954,006	16.1
2021	1,064,001	17.9
2022	1,014,192	17.1
First half of 2023	551,801	9.3
Region		
Beijing	1,110,187	18.7
Shanghai	958,171	16.2
Guangzhou	1,400,266	23.6
Hangzhou	693,290	11.7
Chengdu	338,935	5.7
Tianjin	364,484	6.2
Zhengzhou	345,553	5.8
Shenyang	563,371	9.5
Harbin	153,916	2.6
Any hospitalization		
Inpatient	2,743,931	46.3
Outpatient	3,184,242	53.7
Department visited		
Cardiology	2,417,501	40.8
Geriatrics	410,590	6.9
Neurology	274,813	4.6
Endocrinology	235,001	4.0
Others	2,590,268	43.7

while the usage among patients aged 0–17 was the lowest, at only 0.7%. Males represented 57.0% of the patients, while females accounted for 43.0%. From 2018 to the first half of 2023, the number of prescriptions for beta-blockers showed no significant fluctuations each year. There were notable differences in the number of beta-blocker prescriptions across different regions. Areas with rich medical resources, such as Guangzhou, Beijing, and Shanghai, had higher patient visits, accounting for 23.6%, 18.7%, and 16.2%, respectively. The largest number of prescriptions came from cardiology, accounting for as much as 40.8%.

Usage of different beta-blockers

In Fig. 2, it could be observed that metoprolol dominated among the commonly used beta-blockers, accounting for as much as 62.2%, with its prescription numbers significantly higher than those of other medications. Bisoprolol

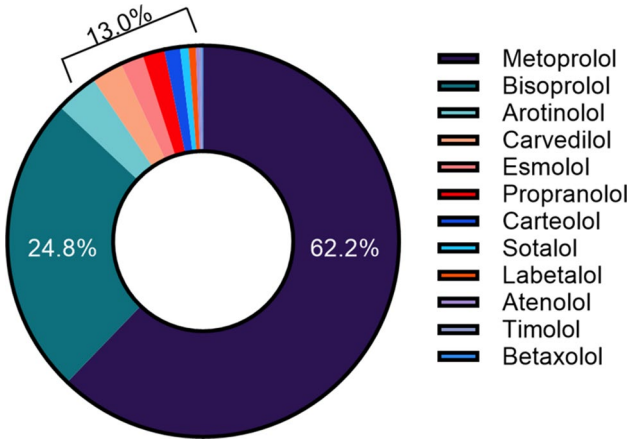

Fig. 2 This figure illustrates the percentage distribution of various beta-blockers among all prescriptions extracted in this study. The data shows that metoprolol is the most commonly used beta-blocker, followed by bisoprolol, atenolol, and carvedilol. Each color represents a different beta-blocker

ranked second with a share of 24.8%, while other drugs showed a significant disparity, each accounting for less than 5%. Bevantolol was not shown in the figure due to its prescription count of only 3.

Diagnostic distribution of different beta-blockers

As shown in Table 4, metoprolol, bisoprolol, arotinolol, carvedilol, labetalol, esmolol, atenolol, and bevantolol were primarily used for the treatment of hypertension. Additionally, carteolol, timolol, and betaxolol were commonly used as ophthalmic medications for ocular hypertension, collectively accounting for more than 90% of prescriptions in this category. Sotalol was most frequently prescribed for arrhythmias, which aligned with its approved indications in the labels, primarily targeting ventricular arrhythmia, atrial flutter, and supraventricular tachycardia. However, it was important to note that sotalol had not been approved for the treatment of hypertension. Nonetheless, 18.25% of prescriptions still indicated hypertension as a diagnosis, which raised concerns about appropriateness. Esmolol showed a significant proportion of prescriptions for hypertension, heart failure, and angina pectoris, with ratios exceeding 10%. However, indications for angina and heart failure had not been approved domestically or internationally, and the label explicitly stated that esmolol should not be used in cases of decompensated heart failure. It was noteworthy that the proportion of propranolol prescriptions that included a diagnosis of hyperthyroidism was 63.72%, significantly higher than that of other beta-blockers.

Basic characteristics of ADE reporting

Table 5 showed that most of the ADE reports were incomplete. For both metoprolol and bisoprolol, the

Table 4 Distribution of common indications of different beta-blockers

Generic name (ICD-10)	Diagnostic proportion (%)												
	Metoprolol	Bisoprolol	Arotinolol	Carvedilol	Labetalol	Esmolol	Carteolol	Propranolol	Sotalol	Timolol	Atenolol	Betaxolol	Bevantolol
Essential (primary) hypertension (I10)	28.50	38.45	63.44	52.08	84.84	16.42	3.31	11.57	18.25	4.80	29.67	1.76	100.00
Cardiac arrhythmia, unspecified (I49.9)	7.92	7.05	3.11	5.66	2.71	9.98	0.28	11.52	44.55	0.40	18.49	0.38	0.00
Angina pectoris (I20)	7.55	5.09	2.49	1.28	1.41	12.94	0.13	[illegible].47	2.37	0.24	11.59	0.00	0.00
Heart failure (I50)	6.24	4.86	3.09	7.38	1.95	14.98	0.14	1.94	2.69	0.22	4.40	0.00	0.00
Acute myocardial infarction (I21)	2.96	1.47	0.32	0.59	0.07	4.71	0.02	0.16	0.40	0.02	0.79	0.00	0.00
Hyperthyroidism (E05)	0.66	0.60	0.12	0.07	1.11	0.32	0.25	63.72	0.88	0.43	0.43	0.25	0.00
Dissection of aorta (I71.0)	0.71	0.22	0.27	0.23	0.39	11.21	0.00	0.12	0.10	0.00	1.34	0.00	0.00
Hypertrophic cardiomyopathy (I42.1, I42.2)	0.30	0.14	0.05	0.07	0.10	0.54	0.01	0.07	0.16	0.02	0.14	0.00	0.00
Ocular hypertension (H40.0)	0.04	0.04	0.04	0.05	0.15	0.04	93.35	0.06	0.01	90.63	0.05	96.23	0.00
Cardiac neurosis (F45.3)	0.03	0.03	0.01	0.01	0.02	0.00	0.00	0.04	0.00	0.04	0.01	0.00	0.00
Migraine (G43)	0.02	0.02	0.02	0.01	0.03	0.00	0.00	1.21	0.01	0.02	0.04	0.00	0.00

Note: The pink highlighted section refers to the approved indications in the National Medical Products Administration (NMPA) or the Food and Drug Administration (FDA) labels.

Table 5 Basic characteristics of ADE reporting for metoprolol and bisoprolol

Characteristics	Number of reports, no. (%)	
	metoprolol	bisoprolol
Age		
0–17	877(1.3)	295(0.7)
18–44	4272(6.4)	1404(3.2)
45–59	7860(11.8)	2804(6.3)
>60	19,803(29.7)	16,094(36.4)
Unknown or missing	33,846(50.8)	23,627(53.4)
Sex		
Female	24,271(36.4)	11,953(27.0)
Male	18,998(28.5)	10,136(22.9)
Unknown or missing	23,389(35.1)	22,135(50.1)
Reporting time		
2004.1-2014.12	18,215(27.3)	3086(7.0)
2015.1-2018.12	20,169(30.3)	11,130(25.2)
2019.1-2024.3	28,274(42.4)	30,008(67.9)
Country	31,259(55.7)	629(2.6)
The United States		
Canada	2177(3.9)	2135(8.9)
Germany	3415(6.1)	2187(9.1)
The United Kingdom	173(0.3)	317(1.3)
Sweden	980(1.7)	141(0.6)
Unknown or missing	18,129(32.3)	18,715(77.6)

highest number of ADE reports came from patients aged over 60, accounting for 29.7% and 36.4%, respectively. There was a higher representation of females in the reports. The number of ADE reports was highest during the period from January 2019 to March 2024. For metoprolol, the majority of ADE reports came from the United States, accounting for 55.7%. In contrast, bisoprolol had a significant amount of missing data; however, Germany had the highest reported cases among the countries with available data, accounting for only 9.1%.

ADE signal analysis

According to Fig. 3, bradycardia, hypotension, and dizziness were the three most reported adverse reactions among the eight beta-blockers, with a total of 3778, 3264, and 2802 cases, respectively. The corresponding SOC were cardiac arrhythmias, vascular disorders, and nervous system disorders. The top 10 PT corresponded to the following SOC: Cardiac Disorders (4), General Disorders and Administration Site Conditions (2), Cardiac Arrhythmias (1), Vascular Disorders (1), Nervous System Disorders (1), and Psychiatric Disorders (1). Metoprolol had the highest proportion of reported cases for all three adverse reactions, with rates of 29.9%, 31.4%, and 43.6%, respectively. Additionally, bisoprolol ranked second in the proportion of bradycardia reports at 23.9%, while carvedilol ranked second for hypotension and dizziness at 18.6% and 26.3%, respectively.

Figure 4 revealed distinct patterns in the ADRs associated with three categories of beta-blockers. The color intensity, reflecting the ROR and the number of reports, suggested that while all beta-blockers carried some risk of adverse events, the frequency and severity differed significantly across the different agents. Additionally, during

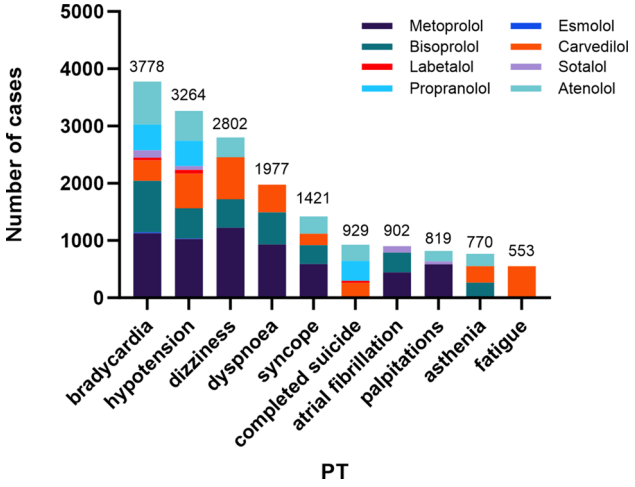

Fig. 3 Distribution of the top ten reported adverse events associated with different beta-blockers. The stacked bar chart shows the number of cases (y-axis) for the top ten Preferred Terms (PT) related to adverse events (x-axis). Each color within the bars represents a different beta-blocker. The total number of cases for each PT is labeled at the top of each bar

the analysis of adverse signals for the eight different beta-blockers, some adverse reactions were identified that simultaneously met the criteria of ROR ≥ 5 and $n \geq 50$, but were not mentioned in the product labeling. For instance, both metoprolol and carvedilol were found to be associated with BRASH syndrome, with metoprolol reporting 186 cases (ROR = 391.285) and carvedilol reporting 72 cases (ROR = 256.459). Although labetalol could be used for hypertension in pregnancy, it was associated with 110 reported ADEs involving premature birth, yielding an ROR of 91.385. Bisoprolol had 247 reported cases of acute kidney injury, with an ROR of 5.641. Moreover, propranolol was linked to 254 reported cases of sleep disorder, which corresponded to an ROR value of 10.98.

Discussion

The study conducted an analysis of the usage and safety of beta-blockers in the real world based on two large databases: the Hospital Prescription Analysis Collaborative Project in China and the FAERS database. The sample was diverse and the time span was extensive, ensuring the representativeness of the results and the statistical reliability.

Analysis of prescription proportions of different beta-blockers

The study indicated that metoprolol was the most commonly used beta-blocker, with excellent efficacy in treating CVDs and relatively few side effects. Metoprolol's high bioavailability and wide volume of distribution enable effective absorption and greater tissue reach, enhancing its overall therapeutic efficacy. The metabolism of metoprolol is significantly influenced by the CYP2D6 enzyme [12]. By understanding a patient's CYP2D6 genotype, clinicians can consider potential adjustments to metoprolol dosing. While adjustments may not always be necessary, knowing the metabolic capacity can aid in making informed decisions, particularly for patients with extreme phenotypes. Furthermore,

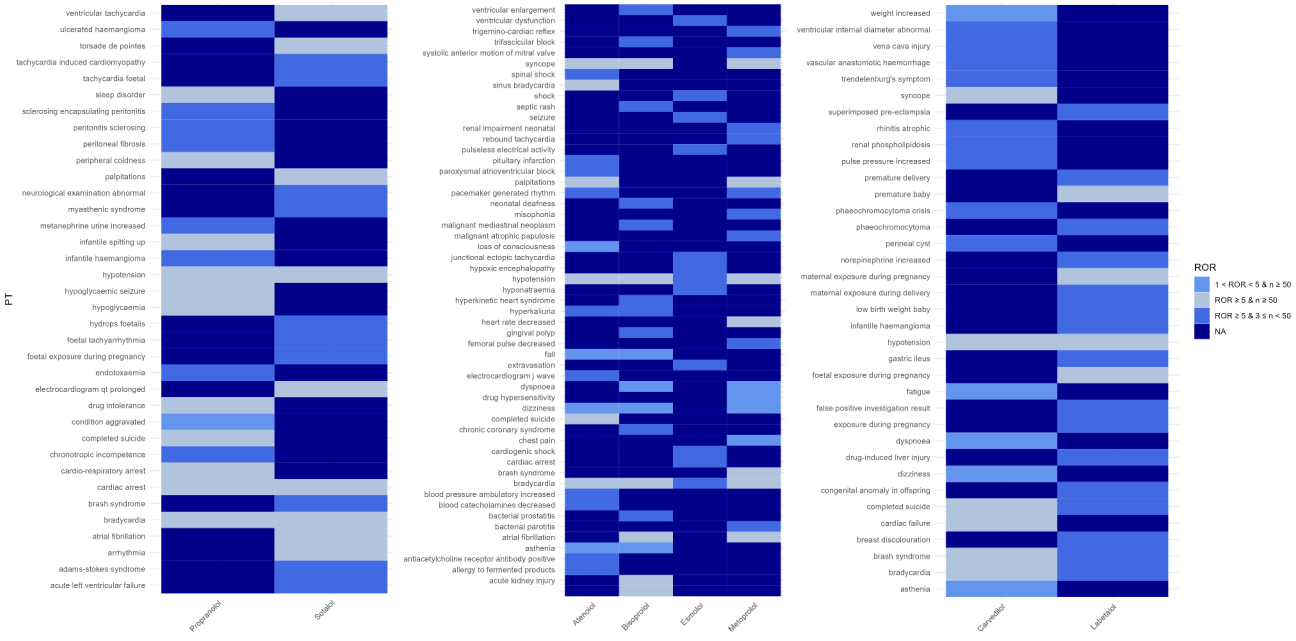

Fig. 4 This heatmap illustrates the ADRs associated with three categories of beta-blockers. Each row represents a different adverse event term (PT), while each column corresponds to a specific beta-blocker agent. The color intensity reflects both the ROR and the number of reports for each ADR, providing a visual comparison of the safety profiles of these beta-blockers

metoprolol is available in multiple formulations, offering flexibility in administration that can accommodate diverse patient preferences and treatment regimens [13]. These pharmacokinetic advantages contributed to its dominant position in the treatment of CVDs. Previous studies discovered that metoprolol had the ability to weaken neutrophil function and decrease neutrophil capillary plugging [14]. The researchers suggested that this effect could potentially play a causative role in reducing infarct size by minimizing coronary microvascular obstruction. Additionally, prior research evaluated the impact of three different beta-blockers (metoprolol, atenolol, and propranolol) using an anesthetized mouse model with 45 min of coronary occlusion/24-hour reperfusion. Only metoprolol demonstrated a reduction in both infarct size and inflammatory response [15]. Propranolol, because of its non-selective beta-adrenergic receptor-blocking action, was associated with a higher incidence of adverse effects, such as sedation and respiratory symptoms. As a result, its clinical use was relatively infrequent. In addition, the relatively low usage rate of labetalol was primarily due to its approved indications being restricted to hypertension, particularly in cases of pregnancy-related hypertension. Additionally, studies showed that the use of labetalol was limited to hypertensive emergencies and urgencies because of its complex pharmacology and short half-life [16].

Analysis of basic characteristics of prescriptions

Aging is closely related to the increasing burden of diseases, particularly CVDs. The major risk factors for CVDs, such as ischemic heart disease, arrhythmias, and cardiomyopathy, have significant prevalence among the elderly [17]. The widespread use of beta-blockers in the cardiovascular field may have contributed to their significant prevalence among elderly patients. However, hypertension guidelines did not recommend beta-blockers for elderly patients unless there were other indications [18]. Clinicians had to balance factors such as comorbidities, patient preferences, and life expectancy. Therefore, the use of beta-blockers in elderly patients remained controversial. Although the prescription rate of beta-blockers for patients aged 0–17 years was relatively low, many doctors still used beta-blockers in pediatric patients. However, none of the various types of beta-blockers were recommended for use in children and adolescents according to their labels, which should be taken into consideration in clinical practice. In fact, the use of beta-blockers in pediatric and adolescent patients was quite common. A cross-sectional observational study focused on patients with hyperthyroidism included 54 subjects with an average age of 11.9 years, of whom 79.6% received treatment with beta-blockers [19]. A single-center retrospective study investigated the dosage, safety, and efficacy of sotalol in neonatal arrhythmias. The median dose required for rhythm control of supraventricular tachycardia (SVT) was 8.5 mg/kg/day or 120.7 mg/m^2/day, with a low incidence of adverse reactions [20]. While there was insufficient evidence to propose a dosing regimen for beta-blockers in children with congestive heart failure, the scant available data indicated that these children might have gained benefits from beta-blocker treatment [21].

The cardiology department was the specialty that prescribed beta-blockers the most, which aligned with the broad range of approved indications for CVDs. Beta-blockers had robust evidence supporting their use in the treatment of various CVDs. A large real-world study demonstrated that beta-blockers were associated with a reduced risk of hospitalization for heart failure and mortality in patients with heart failure with mildly reduced ejection fraction (HFmrEF) [22]. In patients with stable coronary artery disease who did not have heart failure or a recent myocardial infarction, beta-blockers could have reduced the incidence of cardiovascular events over five years [23]. Additionally, any dosage of beta-blockers was significantly associated with a lower mortality rate following acute myocardial infarction. Doses exceeding 25-50% of the recommended target dose were correlated with a greater reduction in the maximum mortality rate within one year after acute myocardial infarction [24]. However, recent studies have shown that in patients experiencing acute myocardial infarction who undergo early coronary angiography and have preserved left ventricular ejection fraction (≥50%), long-term treatment with beta-blockers does not lead to a reduction in the risk of composite primary endpoints of all-cause mortality or new myocardial infarction [25].

In addition to cardiology, the number of prescriptions for beta-blockers was also high in departments such as geriatrics and neurology. This was largely due to the fact that elderly patients often had multiple chronic conditions, including hypertension, coronary artery disease, and heart failure [17], all of which were indications for beta-blocker therapy. In neurology, beta-blockers were commonly used to treat migraines and anxiety disorders. Migraines were a type of primary headache within the nervous system, and patients with migraines had higher rates of hypertension and myocardial infarction [26], making beta-blockers suitable for preventive treatment [27]. Although some cohort studies have shown no consistent relationship between beta-blockers and mental health outcomes [28], most research still recommends their use in alleviating anxiety [29]. Therefore, the application of beta-blockers across various departments reflected their significance and practicality in treating a range of conditions. However, prescription practices in other departments required further analysis to determine whether there was a risk of misuse. The prescriptions issued outside of cardiology needed to

be evaluated to ensure there was sufficient clinical evidence supporting their use and that they complied with the latest treatment guidelines.

Diagnostic rationality analysis

The diagnostic usage proportions of various beta-blockers generally aligned with the indications approved in their prescribing information in China. For example, the new drug bevantolol was approved for the indication of primary hypertension, and although the total number of prescriptions was low, all were associated with a diagnosis of hypertension. The guidelines recommended only three beta-blockers—metoprolol, bisoprolol, and carvedilol—for the treatment of heart failure [30]. However, this study included various medications, such as arotinolol and sotalol, in prescriptions that contained the diagnosis of heart failure. Furthermore, the label explicitly stated that severe or acute heart failure was a contraindication for propranolol. Although animal studies had shown that low-dose propranolol could exert cardioprotective effects by downregulating FGF-23 and improving hemodynamic parameters in a super-acute catecholamine-induced heart failure model in mice, attention needed to be paid to the appropriate selection of beta-blockers to avoid safety concerns [31]. Additionally, although propranolol has not yet been approved for the indication of infantile hemangioma, its efficacy has been widely demonstrated. Randomized controlled trials showed that oral atenolol had similar efficacy to propranolol in the treatment of infantile hemangioma, with fewer adverse events, and could have been considered as an alternative treatment option [32]. Meanwhile, the guidelines recommended that when systemic treatment was necessary, propranolol should be the medication of choice, administered at a dosage of 2 to 3 mg/kg per day. For specific small, thin, and superficial infantile hemangiomas, the use of topical timolol might have been appropriate [33]. Although the use of beta-blockers for treating infantile hemangiomas was considered off-label, it was still deemed reasonable.

Adverse reaction analysis

The majority of beta-blocker prescriptions were given to male patients, but the ADEs predominantly involved female patients. Besides potential bias from missing data, another possible reason for the gender difference was that prescription data mainly came from Chinese sources, while adverse reaction reports were primarily from foreign data. This variation may reflect population differences. The top 10 PTs identified in this study were all adverse reactions mentioned in the drug labels. The pharmacological mechanism of beta-blockers led to their blood pressure-lowering and heart rate-reducing effects; however, caution should be exercised regarding dosage, as excessive use could have led to hypotension and bradycardia. Although the adverse effect of hypotension was common among eight different beta-blockers, studies revealed that only carvedilol and labetalol could cause postural hypotension at higher doses because their alpha-blocking activity promoted vasodilation [16]. Furthermore, lipophilic beta-blockers (such as metoprolol and propranolol) could have penetrated the blood-brain barrier, affecting the central nervous system. This might have resulted in a range of central nervous system-related symptoms, including but not limited to hallucinations, delirium, fatigue, and sleep disorders [34].

It is noteworthy that 929 cases of adverse reactions reported completed suicide, which might have been related to the depressive adverse reactions associated with beta-blockers. A case-control study found that short-term use of beta-blockers was associated with an increased risk of developing depression, particularly with propranolol, which showed a significant correlation with an increased risk of depression. However, studies have shown that long-term use is not associated with an increased risk of depression [35], therefore, caution should be exercised when prescribing beta-blockers to patients with depression. However, some meta-analyses have indicated that, despite clinicians' concerns about the risk of depression, the incidence of depression in patients receiving beta-blocker treatment is not higher than in those receiving placebo [36]. Thus, it was clear that whether beta-blockers caused depression remained a topic of debate, and some studies suggested that beta-blockers might have been misinterpreted as causing depression, whereas the depressive symptoms might have actually arisen from other health issues or treatment indications of the patients [37].

The adverse reactions identified in this study that were not mentioned in the product labeling raised concerns. Regarding the ADE of acute kidney injury (AKI) mentioned in this study, although some research indicated that preoperative use of non-selective beta-blockers (NSBBs) was not associated with AKI after living donor liver transplantation [38], animal studies also suggested that landiolol might have protected renal cells and tissues by inhibiting oxygen consumption and hypoxia-induced by TNF-α in renal cells [39]. However, other studies pointed out that the use of NSBBs was associated with stage 2 AKI in children with class C liver cirrhosis, indicating that caution should be exercised when using NSBBs in this population [40]. BRASH syndrome, defined by bradycardia, renal failure, atrioventricular nodal blockade, shock, and hyperkalemia, was identified as a clinical condition characterized by the simultaneous occurrence of these symptoms. Newly defined as a syndrome in 2016, it warrants additional attention due to its unique presentation. The reduction of cardiac output due to bradycardia can impair renal perfusion, potentially resulting in renal failure and aggravating hyperkalemia. If left unmanaged, this cycle

may escalate into multiorgan failure, characterized by shock, bradycardia, and renal failure [41]. Metoprolol and carvedilol were the most common beta-blockers that triggered BRASH syndrome [42]. Instead of targeting individual aspects like electrolyte disturbances, treatment should be guided by recognizing the full syndrome [43]. Clinicians should be especially cautious when prescribing beta-blockers to patients with renal impairment. The ADEs of propranolol commonly occurred during the treatment of infantile hemangiomas, so special caution needed to be exercised when it was used in children. Propranolol was a lipophilic beta-blocker with high permeability across the blood-brain barrier, which made it more likely to cause sleep disorders. Additionally, the blood-brain barrier in infants was not fully developed and had selective permeability, which likely further enhanced drug penetration and led to a greater occurrence of sleep disorders in infants treated with propranolol for vascular lesions [44]. Although labetalol was the preferred medication for gestational hypertension and was considered to be relatively safe [45], prolonged maternal exposure to labetalol was linked to the occurrence of preterm infants. The identified underlying mechanisms included labetalol's effects on the vascular system, the sympathetic nervous system, and tissue oxygen extraction [46].

Limitations

The limitations of this study were mainly reflected in the following aspects. The diagnostic information from the Hospital Prescription Analysis Collaborative Project might have issues with irregular or incomplete recording. Additionally, the research was primarily based on prescription data and lacked tracking and documentation of patient treatment outcomes. Furthermore, the Hospital Prescription Analysis Collaborative Project only included data from certain provinces in China, which limited its relevance to other countries and constrained a comprehensive understanding of the application value of beta-blockers in clinical practice. Although the FAERS database was a valuable resource that contained a large number of adverse event reports, it relied on voluntary reporting, which might result in incompleteness and bias in the reports. Moreover, both databases exhibited temporal lags. Another important limitation of our study was that it did not include a comprehensive analysis of related subpopulations across different compounds concerning factors such as comedication, physiology, age, and weight. Future studies may benefit from incorporating such subgroup analyses to enhance understanding of the observed signals.

Conclusions

Metoprolol held an absolute dominant position in the use of beta-blockers in China. The off-label use of medications such as sotalol for hypertension and esmolol for heart failure and angina should be guided by clear clinical protocols to ensure appropriate usage in practice. While elderly patients constitute the majority of users, the appropriateness of this practice still warrants further investigation. When using beta-blockers, it was important to carefully monitor the newly discovered adverse reactions, such as the risk of acute kidney injury associated with bisoprolol, as well as the likelihood of BRASH syndrome with metoprolol and carvedilol.

Author contributions

Yilong Yan: Writing—original draft, Writing—review & editing, Methodology, Conceptualization. Wenshuo An: Writing—original draft, Methodology, Data curation, Visualization. Shenghui Mei: Writing—review & editing, Visualization. Qiang Zhu: Writing—review & editing, Formal analysis. Cao Li: Writing—review & editing, Visualization. Li Yang: Writing—review & editing, Supervision. Zhigang Zhao: Writing—review & editing, Supervision. Jiping Huo: Writing—review & editing, Supervision, Conceptualization. All authors have read and agreed to the published version of the manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Code availability

Available from the corresponding author upon request.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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