Epidemiology of Adverse Events and Medical Errors in the Care of Cardiology Patients

Yoshinori Ohta, MD,* Izumi Miki, MPH,† Takeshi Kimura, MD, PhD,‡ Mitsuru Abe, MD, PhD,§ Mio Sakuma, MD, MPH, PhD,|| Kaoru Koike, MD, PhD,¶ and Takeshi Morimoto, MD, MPH, PhD||

OBJECTIVES: There have been epidemiological studies of adverse events (AEs) among general patients but those of patients cared by cardiologist are not well scrutinized. We investigated the occurrence of AEs and medical errors (MEs) among adult patients with cardiology in Japan.

METHODS: We conducted a cross-sectional study of adult outpatients at a Japanese teaching hospital from February through November 2006. We measured AE and ME incidents from patient report, which were verified by medical records, laboratory data, incident reports, and prescription queries. Two independent physicians reviewed the incidents to determine whether they were AEs or MEs and to assess severity and symptoms.

RESULTS: We identified 144 AEs and 30 MEs (16.3 and 3.9 per 100 patients, respectively). Of the 144 AEs, 99 were solely adverse drug events (ADEs), 20 were solely non-ADEs, and the remaining 25 were both causes. The most frequent symptoms of ADEs were skin and allergic reactions due to medication. The most frequent symptoms of non-ADEs were bleeding due to therapeutic interventions. Among AEs, 12% was life threatening. Life-threatening AEs were 25% of non-ADEs and 5% of ADEs (P = 0.0005). Among the 30 MEs, 21MEs (70%) were associated with drugs.

CONCLUSIONS: Adverse events are common among cardiology patients. Adverse drug events were the most frequent AEs, and non-ADEs were more critical than ADEs. Such data should be recognized among practicing physicians to improve the patients’ outcomes.

KEY WORDS: adverse drug event, adverse event, epidemiology, medical error, patient safety, cardiology

Injuries due to medical care, referred to as adverse events (AEs), are an important medical issue because they place an additional burden on the health care system and are associated with symptoms ranging from slight illness to death. Vincent et al. have observed that AEs occur frequently, at the rate of 11% of hospitalized patients. In the U.S., adverse drug events (ADEs) have been reported to occur in 3.9 events of hospitalized cardiac patients per 100 patients. Gandhi et al. found a higher incidence in a prospective cohort study of adult outpatients where 25 of 100 outpatients experienced ADEs in the U.S., which represent the most frequent cause of injury due to medical care in developed countries, and implied that ADEs occur more frequently among outpatients than hospitalized patients.

Adverse events can be either preventable or unpreventable, and preventable AEs are associated with medical errors (MEs). In 2000, the Institute of Medicine (IOM) estimates that MEs kill between 44,000 and 98,000 people every year in U.S. hospitals. James reported updated estimate that a lower limit of 210,000 deaths per year was associated with preventable AEs in U.S. hospitals. Phillips et al. reported that from 1983 to 1993, the number of outpatient visits in the U.S. increased by 75% and ME deaths rose 8.48-fold (from 172 to 1459).

However, studies of AEs among outpatients and studies using patient reporting of AEs are limited. Therefore, we conducted a cross-sectional survey using patient reporting of AEs among adult Japanese cardiovascular outpatients and investigated AEs and MEs during their hospitalization and ambulatory care.

METHODS

Study Design and Patients

We conducted a cross-sectional study at a Japanese teaching hospital equipped with electronic medical records and computerized physician ordering entry. The computerized physician ordering entry did not offer default doses and did not perform automatic checks for allergies or drug interactions.

We included all consecutive patients aged 18 years or older who visited the cardiovascular outpatient clinic of Kyoto University Hospital from February through November 2006. The cardiovascular outpatients include all outpatient visits, including initial consultation, examinations, and postoperative follow-up. Research assistants who were trained by the investigators in an identical manner conducted the survey using the questionnaire (Supplemental Digital Content 1, http://links.lww.com/JPS/A45) for each patient at the outpatient clinic. The patients reported AE and ADE for their entire medical history including the past hospital admission, which were both cardiac and noncardiac care. The research assistants reviewed the patients’ medical records to confirm the potential incidents if reported. They also made telephone calls to the patients if any query needed to be clarified.

The institutional review board of Kyoto University Graduate School of Medicine approved the study, and informed consent was obtained from each patient.

Definitions

The primary outcome was AEs, defined as injuries due to medical care. The causes of all AEs were determined, and multiple
causes were permitted. For example, hepatitis C virus infection after emergent blood transfusion against hemorrhage during an operation was considered to be associated with both a drug and an operation. Adverse events were classified by type, ADEs, and non-ADEs. Adverse drug events included AEs caused by medication use, and non-ADEs included decision-making AEs such as misdiagnosis, operation-related AEs, procedure-related AEs such as cardiac catheterization, and other AEs. For example, cough after receiving angiotensin-converting enzyme (ACE) inhibitors with no other apparent cause was considered an ADE due to medication use, whereas peripheral neuropathy after an operation with no other apparent cause was considered an operation-related AE. Although MEs can occur at any step of the medical process and may or may not cause AEs, for the purposes of this study, we considered AEs without MEs as unpreventable and those resulting from MEs as preventable because we assumed that AEs associated with MEs could have been prevented if the errors had been avoided or intercepted. For example, allergy due to an ACE inhibitor in a patient without a history of ACE inhibitor-induced allergic symptoms was not considered to be the result of a medication error but was considered a medication error if the patient had a history of such allergic symptoms. Minor errors in medication use that had little or no potential for harm, for example, when a dose of noncritical medication such as docusate was administered several hours later, were not considered potential ADEs, but rather medication errors. An error that had the potential for harm, for example, a dose of critical medication such as an intravenous antibiotic not being administered, was considered both a medication error and a potential ADE. A potential ADE was defined as a medication error with the potential to cause injury but did not actually do so either because of specific circumstances, chance, or because the error was intercepted and corrected, such as a prescription with an overdose of medication being written by the physician but then intercepted by the pharmacist.

**Data Classification**

The methods of data collection and classification were modified from a previous report. We developed a questionnaire asking patients about their characteristics and any suspicions of AEs or MEs. They also inquired about the details of cardiovascular comorbidities as well as comorbidities listed in the Charlson comorbidity index.

Two independent physician reviewers who were internists without the affiliation with study clinic had enough experience to review AEs and evaluated all incidents and classified them.

### TABLE 1. Patients’ Characteristics

| Variables                      | All (n = 759) n (%) | AEs (n = 124) n (%) | Non-AEs (n = 635) n (%) | P-value |
|--------------------------------|---------------------|---------------------|------------------------|---------|
| Age, mean ± SD, years          | 65 ± 12             | 64 ± 13             | 65 ± 12                | 0.2     |
| Sex                            |                     |                     |                        |         |
| Male                           | 423 (56)            | 70 (56)             | 353 (56)               | 0.9     |
| Medical history                |                     |                     |                        |         |
| Hypertension                   | 369 (49)            | 68 (55)             | 301 (47)               | 0.1     |
| Myocardial infarction          | 93 (12)             | 18 (15)             | 75 (12)                | 0.4     |
| Angina                         | 176 (23)            | 32 (26)             | 144 (23)               | 0.5     |
| Congestive heart failure       | 109 (14)            | 16 (13)             | 93 (15)                | 0.6     |
| Arteriosclerosis               | 57 (8)              | 12 (10)             | 45 (7)                 | 0.3     |
| Cerebral infarction            | 41 (5)              | 5 (4)               | 36 (6)                 | 0.5     |
| Dyslipidemia                   | 157 (21)            | 36 (29)             | 121 (19)               | 0.01    |
| Diabetes                       | 142 (19)            | 15 (12)             | 127 (20)               | 0.04    |
| Osteoporosis                   | 43 (6)              | 8 (6)               | 35 (6)                 | 0.7     |
| Lung disease                   | 14 (2)              | 3 (2)               | 11 (1)                 | 0.6     |
| Gastric ulcer                  | 82 (11)             | 19 (15)             | 63 (10)                | 0.08    |
| Duodenal ulcer                 | 41 (5)              | 6 (5)               | 35 (6)                 | 0.8     |
| Chronic hepatitis              | 23 (3)              | 7 (6)               | 16 (3)                 | 0.06    |
| Malignant tumor                | 122 (16)            | 30 (24)             | 92 (14)                | 0.01    |
| Others                         | 337 (44)            | 60 (48)             | 277 (44)               | 0.3     |
| Outpatient visits to a doctor  |                     |                     |                        | 0.5     |
| >2 times/month                 | 86 (11)             | 17 (14)             | 69 (11)                |         |
| 2 times/month                  | 80 (11)             | 18 (15)             | 62 (10)                |         |
| 1 time/month                   | 208 (27)            | 31 (25)             | 177 (28)               |         |
| 1 time/2 months                | 115 (15)            | 16 (13)             | 99 (16)                |         |
| 1 time/3-6 months              | 82 (11)             | 11 (9)              | 71 (11)                |         |
| <1 time/6 months               | 188 (25)            | 31 (25)             | 157 (25)               |         |
| Pre hospital admission         | 665 (88)            | 116 (94)            | 549 (86)               | 0.03    |
| 1–3 times                      | 415 (62)            | 61 (53)             | 354 (64)               | 0.07    |
| 4–10 times                     | 216 (32)            | 46 (40)             | 170 (31)               |         |
| ≥10 times                      | 2 (1)               | 3 (3)               | 5 (1)                  |         |
| Unknown                        | 26 (4)              | 6 (5)               | 20 (4)                 |         |

SD, standard deviation
Two causes 1 (1) Drug Procedure

Statistical Analysis
For AE and ME, crude rates per 100 patients and their 95% confidence intervals (CIs) were calculated. Continuous variables are presented as mean with standard deviation (SD) values or median with interquartile ranges, and categorical variables are shown as numbers and percentages. Relationships between patients' demographics and AEs were assessed using the Student t test or the Wilcoxon rank sum test when the data were continuous or the χ² test when the data were categorical. To assess associations between ADEs and severity or durability, and setting and severity for AEs, ADEs, or non-ADEs, we used χ² test. We carried out all statistical analysis using JMP version 8 (SAS Institute Inc., Cary, NC). P values of less than 0.05 were considered statistically significant.

RESULTS

Among 1144 eligible patients, 846 (74%) agreed to participate, and valid questionnaire responses were collected from 759 (90%). Among these 759 patients, 423 (56%) were men and the mean age was 65 ± 12 years. Half of the patients had hypertension, and ischemic heart disease and dyslipidemia affected 35% and 21%, respectively. Twenty-seven percent of the patients visited outpatient clinics once a month. Six hundred sixty-five patients (88%) had a history of hospitalization, and 415 patients had been hospitalized less than 4 times (Table 1).

Adverse Events

The patients reported 225 potential incidents in the questionnaires. The kappa score regarding the presence of an AE between reviewers was 0.69. The reviewers identified 144 AEs in 124 patients, and the crude rate per 100 outpatients was 16.3% (95% confidence interval [CI], 13.9–19.1%). Of the 144 AEs, 99 were solely ADEs, 20 were solely non-ADEs, and the remaining 25 were multiple causes (Table 2). Adverse events by type, including those classified as more than one type, were as follows: 120 ADEs (83%), 22 decision-making AEs (15%), 17 operation-related AEs (12%), 5 procedure-related AEs (3%), and 7 others (5%). Patients experienced 66 AEs (46%) during outpatient visits and 78 AEs (54%) during hospitalization. Among the 66 AEs that occurred during outpatient visits, 60 (91%) were ADEs. Among the 78 AEs that occurred during hospitalization, 60 (78%) were ADEs.

None of the AEs were fatal. Fifteen life-threatening AEs occurred in 13 inpatients and 2 in 1 outpatient (Table 3). There were solely ADEs and solely non-ADEs, and 3 multiple causes. Serious and significant AEs accounted for 41 and 86 AEs, respectively. Among the 41 serious AEs, 35 involved ADEs. Among the 86 significant AEs, 78 involved ADEs. Two life-threatening AEs (3%), 18 serious AEs (27%), and 46 significant AEs (70%) occurred during outpatient visits. Fifteen life-threatening AEs (19%), 23 serious AEs (29%), and 40 significant AEs (51%) occurred during hospitalization (Fig. 1). Non-ADEs were more severe than ADEs and longer failure than ADEs (Table 4). Among 144 AEs, 113 AEs (78%) resulted in transient injury and 31 AEs (22%) resulted in permanent injury or injury that compromised the patient’s life.

Allergic or skin reactions were the most frequent symptoms followed by cardiovascular symptoms of all AEs and ADEs. Bleeding was the most frequent symptom followed by allergic

| TABLE 2. Causes of AEs |
|------------------------|
| **AEs (n = 144)** n (%) | **First Cause** | **Second Cause** | **Third Cause** |
| Single cause | | | |
| 99 (69) | Drug | | |
| 14 (10) | Operation | | |
| 2 (1) | Procedure | | |
| 4 (3) | Decision-making | | |
| Two causes | | | |
| 1 (1) | Drug | Procedure | |
| 12 (8) | Drug | Decision making | |
| 6 (4) | Drug | Other | |
| 2 (1) | Operation | Decision making | |
| 2 (1) | Procedure | Decision making | |
| Three causes | | | |
| 1 (1) | Drug | Operation | Decision making |
| 1 (1) | Drug | Decision making | Other |
Medical Errors

We identified 30 MEs among 30 patients; the incidence rate was 3.9 (95% CI, 2.8%–5.6%) per 100 patients. Among the 30 MEs, 29 resulted in AEs, meaning that 20% of the 144 AEs were considered preventable. Among the 29 MEs with AEs, 4 MEs (14%) resulted in life-threatening AEs, 12 (41%) in serious AEs, and 13 (45%) in significant AEs. The other ME did not result in AE. This event was a medication error, which had the potential to harm the patient; however, this medication error was intercepted before the drug was administered. Among 30 MEs, 18 MEs (60%) were associated with drugs (Table 6). Fifteen MEs occurred during outpatient visits (50%) and 15 occurred during hospitalization (50%). Among the 15 MEs during outpatient visits, 8 were associated with drugs. Among the 15 MEs during hospitalization, 10 were associated with drugs.

DISCUSSION

Studies concerning patient reporting of AEs were limited. Recently, efforts to use patient-reported information would be more important. Yelp jointed with ProPublica are utilized and give consumers satisfaction with medical care. In the United States, a new system for patients to report medical mistakes was constructed. The Obama administration wants consumers to report medical mistakes and unsafe practices by doctors, hospitals, pharmacists, and others who provide treatment.

We assessed the frequency of AEs and MEs in daily practice in Japan and found that they occur often and cause substantial harm. The crude rate of AEs was 16 per 100 outpatients, and 20% of AEs were associated with MEs. Among the 144 AEs, 120 (83%) were ADEs and 51 (35%) were non-ADEs including 17 surgical AEs (12%). Seven ADEs (6%) and 8 surgical AEs (47%) were life-threatening. Adverse drug events were more frequent in outpatients, and surgical AEs were the most dangerous. Although the symptoms among non-ADEs were different, the symptoms among ADEs were similar; allergic or skin reactions were the most frequent symptoms among all ADEs, followed by cardiovascular and gastrointestinal symptoms.

TABLE 3. Details of Life-Threatening AEs (n = 17)

| Details                                | No. of AEs |
|----------------------------------------|------------|
| ADEs                                   |            |
| Anaphylactic shock                     | 2          |
| Steven Johnson syndrome                 | 1          |
| Loss of consciousness or syncope       | 2          |
| Syncope due to delayed diagnosis       | 1          |
| Non-ADEs                               |            |
| Poor communication about drug with known allergy (multiple causes) | 1          |

TABLE 4. Relationship Between AEs and Severity or Outcome

| Severity                          | ADEs (%) | Non-ADEs (%) | P     |
|-----------------------------------|----------|--------------|-------|
| Life threatening                  | 7 (6)    | 13 (25)      | 0.0003|
| Serious                           | 35 (29)  | 17 (33)      | 0.6   |
| Significant                       | 78 (65)  | 21 (41)      | 0.004 |
| Outcome                           |          |              |       |
| Transient injury                  | 107 (88) | 28 (55)      | 0.6   |
| Permanent injury or injury that compromised the patient’s life | 13 (11)  | 23 (45)      | 0.004 |
Regarding the occurrence of AEs, a systematic review on hospitalized patients found a median rate of 9.2% for AEs and 43.5% for preventable AEs. The occurrence of AEs approximately 20 years ago was fewer than it is now. The Harvard Medical Practice Study I showed 3.7% had AEs. A 1992 study surveying 15,000 patients in Colorado and Utah reported that 3% of patients had AEs. Updated estimate showed 13.5% of surveying 15,000 patients in Colorado and Utah reported that approximately 50% of patients had at least one AE. Overall, at least 44% of these events were judged as being preventable and 51% unpreventable. Landrigan et al reported that among 2341 admissions, internal reviewers identified 588 harms (25.1 harms per 100 admissions) and harms remain common. Merino et al reported that 29% of hospitalized patients had AEs, with 62% not causing any harm. Among the no-harm events, 90% were classified as preventable AEs.

Although methodological differences between these studies and the current study made comparisons difficult, we believe the AE rate in the current study was generally similar to these other reports; however, our ME rate was lower. Because the first step of our methodology was a patient questionnaire, underestimating the incidence of MEs was inevitable. If patients were not aware of MEs that were intercepted or did not cause harm or symptoms, they could not report these in the questionnaire. Another reason why our rate of MEs was lower than that of other recent studies could be due to the increase in awareness of AEs among health care providers. Merino et al reported that the overall rate of AEs was 98% and although surgery-related incidents were few (3%), they were considered to be severe. Our results were consistent with past reports, these symptoms were peculiar to cardiovascular outpatients.

Our study had several limitations. First, because the potential incidents were obtained from patient questionnaires and then verified by physicians, our results may not reflect incidents that occurred of which patients were unaware. In addition, we could not identify the symptoms including dizziness, and gastrointestinal symptoms. If the patients were prescribed new antihypertensive agents and the physician detected hypotension or the patients recovered after self-cessation of them, we diagnosed the conditions of dizziness or fatigue as hypotension due to antihypertensive agents. Although our results were consistent with past reports, these symptoms were peculiar to cardiovascular outpatients.

A systematic review studying ADEs in ambulatory care reported a prevalence of 12.8 per 100 outpatients. Gandhi et al reported that the incidence of ADEs was 27 per 100 outpatients. Cardiovascular agents such as beta-blockers, ACE inhibitors, and calcium-channel blockers were most frequently implicated in these ADEs. Studies from a U.S. ambulatory department reported that cardiovascular medications were the most commonly implicated ADEs. Our results showed that the incidence of cardiovascular symptoms in the outpatient setting was higher than that in the hospital setting, and those cardiovascular symptoms were the second most frequent symptoms of ADEs. Elsewhere, Gandhi et al reported that the most frequent symptoms of ADEs were gastrointestinal followed by sleep disturbances, fatigue, and mood change. Weingart et al reported that the most frequent symptoms of ADEs were gastrointestinal followed by fatigue, dizziness, and rash or itching. We found that the most frequent symptoms of ADE were allergic or skin reactions followed by cardiovascular symptoms including dizziness, and gastrointestinal symptoms. If the patients were prescribed new antihypertensive agents and the physician detected hypotension or the patients recovered after self-cessation of them, we diagnosed the conditions of dizziness or fatigue as hypotension due to antihypertensive agents.

Table 5: Symptoms of AEs

| Symptoms                        | AEs (%) | Non-ADEs (%) | ADEs (%) | ADEs in Outpatient (%) | ADEs in Inpatient (%) |
|--------------------------------|---------|--------------|----------|------------------------|-----------------------|
| Bleeding                        | 12 (8)  | 13 (25)      | 4 (3)    | 3 (5)                  | 1 (2)                 |
| Central nervous system          | 11 (7)  | 4 (8)        | 11 (9)   | 2 (3)                  | 9 (15)                |
| Allergic or skin symptom        | 45 (31) | 9 (18)       | 43 (36)  | 21 (35)                | 22 (36)               |
| Liver disorder or metabolic disorder | 10 (7)  | 2 (4)        | 9 (7)    | 2 (3)                  | 7 (11)                |
| Cardiovascular                  | 26 (18) | 9 (18)       | 22 (18)  | 13 (22)                | 9 (15)                |
| Gastrointestinal                | 13 (9)  | 2 (4)        | 13 (11)  | 9 (15)                 | 4 (7)                 |
| Kidney injury                   | 1 (1)   | 0 (0)        | 1 (1)    | 1 (2)                  | 0 (0)                 |
| Respiratory                     | 5 (3)   | 0 (0)        | 5 (4)    | 4 (7)                  | 1 (2)                 |
| Bone marrow depression          | 3 (2)   | 1 (2)        | 3 (2)    | 0 (0)                  | 3 (5)                 |
| Others                          | 18 (12) | 11 (22)      | 9 (7)    | 5 (8)                  | 4 (7)                 |

Table 6: Details of MEs

| Causes                        | Type of Error             | Medical Errors (n = 30) n (%) |
|-------------------------------|---------------------------|------------------------------|
| Drug                          | Wrong action against the symptoms | 11 (37)                     |
|                               | Different drug            | 2 (7)                        |
|                               | Ignoring interaction      | 1 (3)                        |
|                               | Wrong dose                | 1 (3)                        |
|                               | Omission                  | 2 (7)                        |
|                               | Wrong route               | 1 (3)                        |
|                               | Drug with known allergy   | 1 (3)                        |
| Operation                     | Inappropriate operation   | 3 (10)                       |
| Procedure                     | Inappropriate procedure   | 5 (17)                       |
| Decision making               | Misdiagnosis              | 4 (13)                       |
not obtain potential incidents associated with fatalities; thus, we might have missed critical and severe AEs and MEs. Indeed, there were no fatal AEs in our study. Second, the patients were from a single cardiovascular clinic of a teaching hospital. Although the sample was sufficiently large to allow reasonably accurate estimates of AE and ME incidence, the results might not be generalizable to other settings. However, our results may be applicable to Japanese outpatients.

CONCLUSION
We showed that AEs were common among cardiology patients. Adverse drug events were the most frequent AEs, and non-ADEs were more critical than ADEs. Adverse events and non-ADEs were more severe in hospitalized patients than in outpatients. The proportion of MEs was significant, and most were related to medication use. Such data should be recognized among practicing physicians to improve the patients’ outcomes.

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