Systematic Analysis of the Incidence of Coronary Stent Fracture and Adverse Events in Japan

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Abstract

Coronary stent fracture (SF) is recognized as a risk of restenosis or stent thrombosis. However, the actual incidence is unclear in real world clinical settings in Japan. This study aims to estimate the incidence of SF in Japan by surveying peer-reviewed journals, and to elucidate the actual situation of adverse event reports. We conducted literature analysis regarding the incidence of SF using PubMed and ICHUSHI on April 1 2014. For PubMed, the term "stent fracture" was used. For ICHUSHI, "coronary artery" (in Japanese), "stent" (in Japanese), "fracture" (in English), "fracture" (in Japanese), and "damage" (in Japanese) were used. PubMed search initially yielded 895 papers. Of these, 792 studies had been conducted in countries outside of Japan, 45 studies were related to non-coronary artery, 17 studies did not deal with incidences of SF, and 11 studies targeted duplicated cases during the same implantation period. After these studies were excluded, we analyzed 30 remaining papers comprising 14 observational studies and 16 case reports. There were 643 SF cases in the scientific papers and 105 SF cases in the adverse event reports. Through the 14 observational studies, the SF incidence was estimated as 5.4% (595/10,927 lesions). We found a significant difference in SF incidences between the paper and adverse event report (6.1-fold). These data indicated that the adverse event report showed a partial picture of the real situation.

抄 録

冠動脈ステントの破断は, 再狭窄やステント血栓症のリスクとして認識されている. しかし, 実際の発生頻度は明確になっていない. 本研究は, 查読付き論文を調査することによって国内におけるステント破断の発生状況を評価し, 不具合報告の現状を明らかにすることを目的としている. 2014年4月1日にPubMedおよび医学中央雑誌(医中誌)を用いてステント破断の発生に関する文献分析を実施した. PubMedでは, 「stent fracture」を検索単語として使用した. 医中誌では, 「冠動脈」「ステント」「fracture」「破断」「破損」を検索単語として使用した. PubMed検索で895報が検索された. これらの中で, 日本以外の施設にて実施された文献が792報, 冠動脈が対象ではない文献が45報, ステント破断とは関係のない文献が17報, 同一症例を対象としていると考えられる文献が11報あった. これらを除外し, 14報の観察研究および16報の症例報告で合計30報を解析対象とした. 查読付き論文では643病変でのステント破断, 不具合報告では105病変でのステント破断が報告されていた. 14報の観察研究から, ステント破断の発生頻度は5.4% (10,927病変中595病変) であった. 不具合報告から得られたステント破断の発生件数は, 文献分析によって得られた発生件数より6.1倍少なかった. これらの結果から, 不具合報告によっ
Introduction

Approximately 220,000 coronary stent implantations were conducted in 2012, with drug-eluting stent (DES) implants comprising 80% of all the cases\(^1\). Since the introduction of DES, there has also been a significant reduction in the incidence of restenosis in patients who have undergone percutaneous coronary intervention (PCI) treatment\(^2, 3\). Coronary artery bypass grafting (CABG) is a surgical procedure that is also used in the treatment of coronary artery disease. Studies have reported that the PCI:CABG ratio in the US ranges from 1:1.7 to 1:3.3\(^4, 5\), whereas the ratio in Japan is 13:1\(^6\). These figures indicate the current prevalence of PCI treatment in Japan. Due to increase in aging population in Japan, accumulated number of PCI can be estimated to increase. Therefore, PCI treatment will occupy an increasingly important position for coronary heart disease patients in Japan. Typical adverse events associated with DES include stent thrombosis (ST) and stent fracture (SF). For ST, it has been reported that the long-term prevention of arterial intimal coverage due to the drugs or polymers coating the stent may induce platelet aggregation and thrombosis\(^6\). There are studies that analyze temporal trends in ST occurrences associated with the DES products\(^7\)–\(^11\). SF involves the post-implantation physical fracturing of a stent. The exposed metal surface of a stent fracture site can result in an increased risk of restenosis or ST. The first recorded incidence of SF was reported in 2002\(^12\). Although there have been case reports or observational studies from single institutions documenting SF cases after the introduction of DES\(^13\), the actual situation of coronary SF incidence in Japan remains unclear because large scale prospective studies or registry are unrealistic in terms of cost in real world clinical settings. It is recognized that adverse event reporting system operated by the Pharmaceuticals and Medical Devices Agency and Ministry of Health, Labour and Welfare have limitation in estimating actual situation. The importance of estimating real incidences of adverse events of medical devices in postmarket is common concern in United States\(^14, 15\). This study aims to estimate the incidence of SF in Japan by surveying peer-reviewed journals, and to elucidate the actual situation of adverse event reports.

Methods

1. Analysis of literature on coronary stent fracture incidence in Japan

In order to assess the incidence of coronary SF in Japan, we conducted a literature survey using the PubMed database (managed by the US National Center for Biotechnology Information) and the Igaku Chuo Zasshi (ICHUSHI) bibliographic database (managed by the Japanese Medical Abstracts Society). A flow chart of bibliographic search of coronary SF was shown in Fig. 1. The bibliographic search of PubMed was conducted on April 1, 2014 using the search term “stent fracture”. As this analysis was

Key words: coronary stent, stent fracture, adverse event reporting system
focused on coronary SF that had occurred in Japan, studies were excluded from analysis if they were conducted in other countries or did not target coronary artery. The bibliographic search of ICHUSHI was also conducted on April 1, 2014. The following search terms were used “coronary artery” (in Japanese), “stent” (in Japanese), “fracture” (in English), “fracture” (in Japanese), and “damage” (in Japanese). Studies were excluded from analysis if they fulfilled the same exclusion criteria used in the PubMed search. The results of the PubMed search initially yielded 895 literatures. Of these, 792 studies had been conducted in countries outside of Japan, 45 studies were analyses of non-coronary artery, 17 studies did not deal with incidences of SF, and 11 studies targeted duplicated cases during the same implantation period. After these studies were excluded, there were 30 remaining literatures comprising 14 observational studies and 16 case reports.

The search of the ICHUSHI database initially yielded 47 literatures. Of these, 3 studies had been conducted in countries outside of Japan, 12 studies were classified as “conference abstracts” or “commentary” instead of “original article” or “case report”, 1 study was an analysis of non-coronary artery, 5 studies did not deal with incidences of SF, and a further 5 studies overlapped with literatures obtained from the PubMed search. After these studies were excluded, there were remaining 21 literatures, all of which were case reports.

2. Medical device adverse event reports related to coronary stent fracture cases in Japan

Article 68-10-1 of the act for ensuring etc. the quality, efficacy, and safety of drugs, medical devices, etc. (Hereinafter referred to as the “act...
on drugs, medical devices etc.) stipulates that marketing approval holder of medical devices are required to submit reports regarding cases (or suspected cases) of adverse events to the Minister of Health, Labour and Welfare. Article 68-13-3 of the act on drugs, medical devices etc, and Article 228-23 of the ministerial ordinance for enforcement of the act for ensuring etc. The quality, efficacy, and safety of drugs, medical devices, etc.(Hereinafter referred to as the "ministerial ordinance for enforcement") specifies that these adverse event reports are to be submitted to the pharmaceuticals and medical devices agency (PMDA), Japan. In this analysis, we performed a search of adverse event reports which is available on the PMDA website . This search was conducted on April 30, 2013, and included adverse event reports that had been submitted to the PMDA by October 2012. The following search terms were used “Japanese Medical Device Nomenclature: coronary stent”, “adverse event term: fracture (in Japanese), and damage (in Japanese)”. Reports from device marketing approval holder are made available on the PMDA website after 6 months of receipt. The search revealed that there were 103 adverse event reports of SF cases. In accordance with Japanese law concerning access to information held by independent administrative institutions such as the PMDA, we submitted a request to the PMDA for the disclosure of these reports on April 30, 2013. Approval to release the reports was granted on February 25, 2014, and the reports were made available for analysis on April 1, 2014. Of the 105 adverse event reports, 2 were excluded as they did not include confirmed incidences of SF: the remaining 103 reports were analyzed.

Results

1. Coronary stent fracture incidence in Japan

A total of 51 literatures were analyzed. The results of the literature analysis are presented in Table 1. These studies documented 643 lesions with SF from 10,975 lesions. The 103 adverse event reports obtained from the request for disclosure to the PMDA documented 105 lesions with SF. These results led to a total of 748 coronary SF cases.

2. Analysis of literature on coronary stent fracture incidence in Japan

The analysis of literature on observational studies and case reports showed that coronary SF occurred in 643 of 10,975 lesions. In the 14 observational studies, the incidence of coronary SF was 5.4% (595/10,927 lesions). In these observational studies, post-implantation follow-up (generally conducted at 6-9 months after implantation) using coronary angiography (CAG) was performed in 65.6% of the subjects (8,348/12,724 patients). The most common stent was Cypher (Johnson and Johnson), which accounted for 83.5% of SF documentations (537/643 lesions); this was followed by Nobori (TERUMO) at 9.3% (60/643 lesions) and XIENCE V/PROMUS (Abbott Vascular Japan) at 6.1% (39/643 lesions). The results showed that 31.9% (205 lesions reported in 36 studies) of all the SF cases had reported within 1 year after stent implantation and 80.4% (517 lesions reported in 40 studies) within 2 years (Table 2). Of the 51 literatures reporting cases of coronary SF in Japan, 49 literatures (reporting 583 lesions) involved the investigation of patient statuses at the point where SF had been diagnosed during a sched-
uled follow-up examination: the other 2 litera-
tures (reporting 60 lesions) included further
examination of patient prognoses by investigat-
ing medical records\textsuperscript{17, 18}).

3. Medical device adverse event concern-
ing coronary stent fracture cases in
Japan

An analysis was conducted on the 103 adverse
event reports involving 105 lesions with SF that
had been submitted to the PMDA. The most
common stent was Cypher (Johnson and John-
son), which accounted for 93.3\% of all the docu-
mented lesions with SF (98/105 lesions): this
was followed by TAXUS Express2 (Boston Sci-
cientific Japan) at 2.8\% (3/105 lesions) and
XIENCE V/PROMUS (Abbott Vascular Japan)
at 1.9\% (2/105 lesions). Each remaining case was
associated with a single stent product (Table 1).

![Table 1](attachment:table1.png)

Values are presented as “n (%)”. ICHUSHI, Igaku Chuo Zasshi database; PMDA, Pharmaceuticals and Medical Devices Agency; CAG, coronary angiography; IVUS, intravascular ultrasound; OCT, optical coherence tomography; CT, computed tomography; RCA, right coronary artery; LMCA, left main coronary artery; LAD, left anterior descending artery; LCx, left circumflex artery; BG, bypass graft (including saphenous vein graft and left internal thoracic artery); NA, not available; ISR, in-stent restenosis; TLR, target lesion revascularization. XIENCE V/PROMUS was described as 1 product because an identical product was approved by 2 names.
patients, 74.3% (78/105 lesions) of SF cases were diagnosed within 2 years after implantation (Table 2). Out of all the reports, 97.1% (102/105 lesions) only report the SF incidences at the timing where SF had been diagnosed, and the prognoses were not reported. Patients who had presented with symptoms at the time of diagnosis accounted for 72.4% (76/105 lesions) of all the SF cases; the remaining 29 patients were asymptomatic at the time of diagnosis (Fig. 2). Of these 29 patients, 3 patients developed ST 7–15 months after SF diagnosis. Although the other 26 patients were asymptomatic until the end of the follow-up period, less than 1 year had elapsed since SF diagnosis for 96.2% (25/26 lesions) of the patients.

**Discussion**

1. **Incidence of coronary stent fracture in Japan**

The incidence of coronary SF has been reported to be 0.84–7.7% in sirolimus-eluting stent and paclitaxel-eluting stent\(^{19}\). Our analysis of 14 published observational studies showed the SF incidence rate in Japan to be 5.4% (595/10,927 lesions). Out of all the SF cases, 31.9% (205 lesions reported in 36 studies) of SF cases were found within 1 year and 80.4% (517 lesions reported in 40 studies) of SF cases were found within 2 years. These results suggested that follow-up by 1 year after stent implantation might be not enough to precisely estimate incidence of SF. When including the cases documented in case reports and adverse event reports, there was a total of 748 coronary SFs, 84.9% (635/748 lesions) of which occurred in patients implanted with Cypher that had been discontinued from the market in 2011. Cases involving the Nobori, which had been approved for use in March 2009, accounted for 8.0% (60/748 lesions) of all the SF cases\(^{20}\); cases involving the XIENCE V/PRO-MUS, which had been approved for use in January 2009, accounted for 5.5% (41/748 lesions) of all the SF cases\(^{21}\). This indicates that SF is an adverse event that occurs even among the relatively newer stents (Table 1, Fig. 3). The analysis of the 14 published observational studies revealed that the percentages of post implantation follow-up examination using CAG were 65.6% (8,348/12,724 lesions). This highlights the limitation in accurately ascertaining SF incidence. There were distinct differences in the in-

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stent restenosis, target lesion revascularization, and stent thrombosis incidence between observational study and case report. It might be because these observational studies about SF did not necessarily aim to investigate in-stent restenosis, target lesion revascularization, and stent thrombosis.

2. Difference in stent fracture incidences between the literature analysis and adverse event reports

There were 643 coronary SF cases extracted from the literature analysis in the PubMed and ICHUSHI databases. In contrast, analysis of the adverse event reports obtained from the disclosure request to the PMDA resulted in 105 documented cases. Incidence of SF in the adverse event reports yielded 6.1-fold lower than that in the literature analysis. According to article 68-10-1 and article 68-13-3 of the act on drugs, medical devices etc, and Article 228-23 of the ministerial ordinance for enforcement, marketing approval holder of medical devices must report any adverse events to PMDA. For cases that occur in Japan, serious adverse events (including those that pose a risk of serious adverse events) are subject to mandatory reporting as case reports. Notification from the Director of the Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare,
reduced mortality on October 2, 2014 stated that an adverse event includes "a wide range of defects such as the breaking or malfunctioning of a medical device". According to the act on drugs, medical devices etc., medical personnel shall endeavor to report any adverse events to PMDA. However, all the SF cases were reported by marketing approval holder of medical devices (Fig. 4). The substantial difference in SF incidence (6.1-hold) between the two data sources suggests a lack of awareness of the adverse event reporting system. These differences imply current situation that medical personnel does not recognize SF as a reportable adverse event, and the information is not conveyed to the marketing approval holder. These data indicated the importance of publicizing the adverse event reporting system to medical personnel, and the importance of the literature analysis by marketing approval holder.

3. Study Limitation

The limitations of this study are as follows: in the comparison of SF incidences between the literature analysis and adverse event reports, the latter was limited to reports that had been submitted to PMDA by October 2012. However, the literature analysis was conducted on April 1, 2014. As a result, any reports that had been submitted during this gap could not be included in the analysis. However, when the search on the PMDA website was conducted on October 1,
2014, additional reports after October 2012 were 8. Next, the numbers of SF of different stent products would be partially influenced by approval date.

**Conclusions**

The coronary SF incidence was estimated as 5.4% (595/10,927 lesions) from 14 observational studies. Out of all the SF cases, 31.9% (205 lesions reported in 36 studies) of SF cases were found within 1 year and 80.4% (517 lesions reported in 40 studies) of SF cases were found within 2 years. The results indicated the importance of continuous collection of information about SF, although SF occurrence has decreased in the second-generation DESs. These data indicated that the adverse event reports submitted to PMDA present an incomplete picture of the situation, and importance of publicizing the adverse event reporting system to medical personnel and marketing approval holders.

**References**

8) Serruys PW, Morice MC, Kappetein AP.


