Evaluation of Postmarket Clinical Benefits and Risks of Medium-High Risk Medical Devices

陳建煒 K. Arnold Chan, MD, ScD, FISPE

National Taiwan University (NTU) / NTU Hospital

NTU Health Data Research Center (HDRC)

5th Joint Conference of Taiwan and Japan on Medical Products Regulation

December 1, 2017

Conflict of Interest disclosure

- Deputy Chair, Drug Safety Committee, Taiwan FDA
- Under a grant from the Ministry of Health and Welfare to NTU Hospital, I provide free consultation to private companies in Taiwan to promote the biotechnology industry
- I conduct public domain research sponsored by medical product companies

Benefit and risk …

Contains Nonbinding Recommendations

Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices

---

Guidance for Industry and Food and Drug Administration Staff

Document issued on August 31, 2017.

The draft of this document was issued on July 27, 2016

Real World Evidence

- NOT data from a clinical trial conducted in a referral medical center with the best technology and the sickest patients
- Real World Data
  - Clinic-based **registry** (primary data)
  - Existing health data (secondary data)
    - Health insurance claims
    - Electronic medical records
- Relevant methods

www.ncbi.nlm.nih.gov/books/NBK208616/

Volume 1

Registries for Evaluating Patient Outcomes:

A User's Guide

Third Edition

2017; 376: 526-35

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Registry-Based Prospective, Active Surveillance of Medical-Device Safety

Frederic S. Resnic, M.D., Arjun Majithia, M.D., Danica Marinac-Dabic, M.D., Ph.D., Susan Robbins, B.S., Henry Ssemaganda, M.D., Kathleen Hewitt, M.S.N., Angelo Ponirakis, Ph.D., Nilsa Loyo-Berrios, Ph.D., Issam Moussa, M.D., Joseph Drozda, M.D., Sharon-Lise Normand, Ph.D., and Michael E. Matheny, M.D., M.P.H.

- Vascular closure device after percutaneous coronary intervention through femoral artery (Mynx vs. other products)

N Engl J Med 2017; 376: 526-35

- Using data from an existing surveillance system (Data Extraction and Longitudinal Trend Analysis DELTA)
- Data source – CathPCI Registry of the National Cardiovascular Data Registry
  - 73,164 users of Mynx device
  - 603,437 users of alternative devices
  - Data were prospectively collected from many clinical sites, with very rich clinical information

Resnic FS et al. N Engl J Med 2017;376:526-535

Propensity score method – improve comparability between the two groups

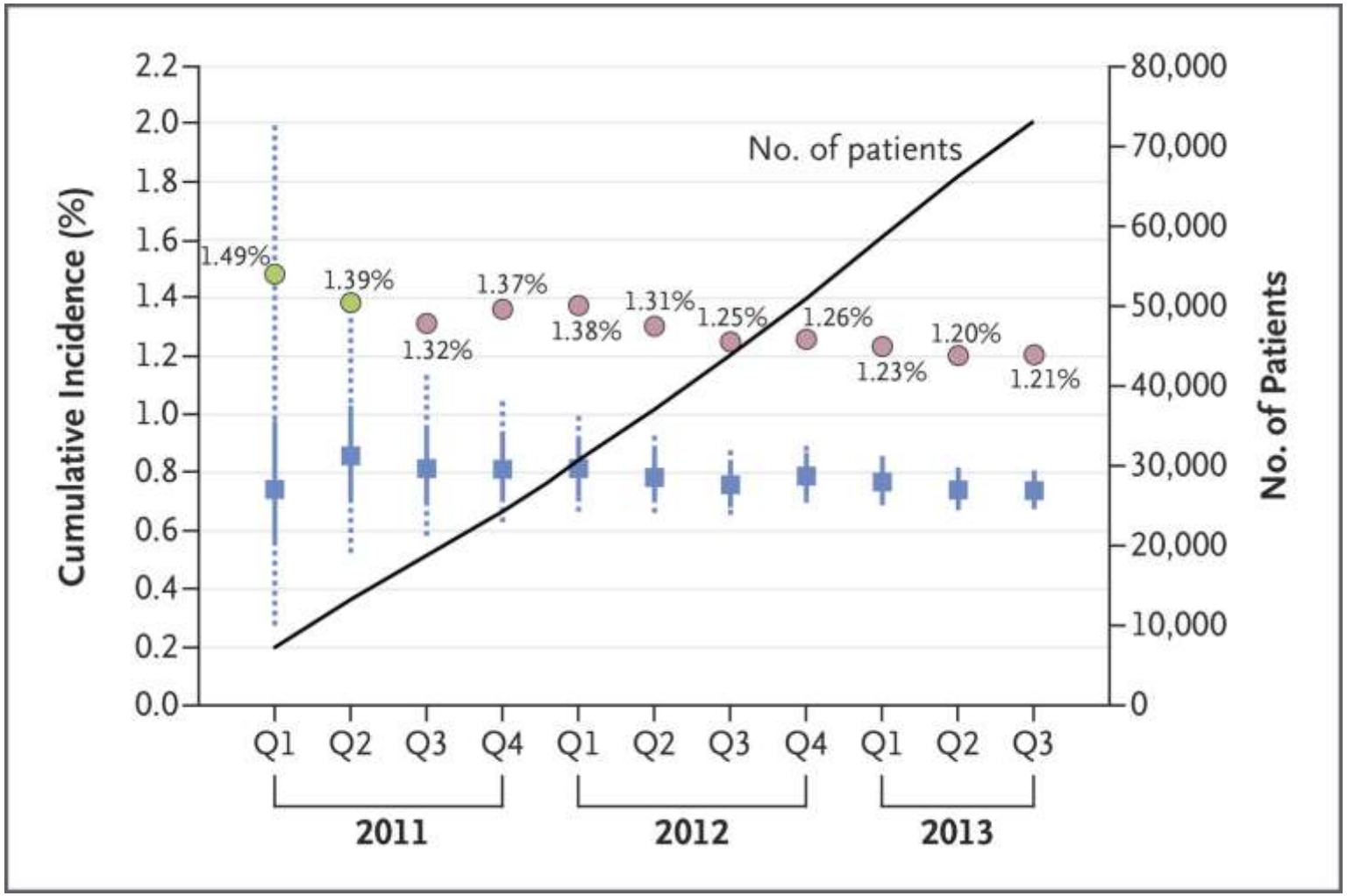
Table 1. Demographic and Clinical Characteristics of the Patients before and after Propensity Matching, According to Receipt of the Mynx Device or Alternative Devices.*

Characteristic	Before Propensity Matching			After Propensity Matching			Unmatched Exposures	
	Mynx Device (N=73,164)	Alternative Device (N=603,437)	Standardized Difference†	Mynx Device (N=73,124)	Alternative Device (N=73,124)	Standardized Difference†	Mynx Device (N=40)	Standardized Difference†
Age (yr)	65.3±11.9	65.1±12.1	0.017	65.3±11.9	65.3±12.0	0.001	64.4±11.9	0.075
Female sex (%)	34.3	30.5	0.081	34.3	34.2	0.002	30.0	0.092
Body-mass index (%)‡								
<21	3.7	3.7	0.002	3.7	3.7	0.002	7.5	0.168
≥21 and <25	15.7	16.1	0.026	15.7	15.7	0.001	15.0	0.046
≥25 and <30	35.4	37.0	0.033	35.4	35.4	0.001	37.5	0.043
≥30	45.2	43.2	0.041	45.2	45.2	0.001	40.0	0.106
Coexisting condition (%)								
Diabetes	39.8	35.9	0.080	39.8	40.2	0.008	45.0	0.105
Chronic lung disease	16.5	13.6	0.081	16.5	16.7	0.003	35.0	0.433
Hypertension	84.8	81.1	0.099	84.8	84.8	0.001	80.0	0.128
Peripheral arterial disease	12.7	9.8	0.092	12.6	12.6	0.001	25.0	0.320
NSTEMI on presentation	18.9	20.3	0.036	18.9	18.9	0.000	27.5	0.205
Laboratory measure								
Baseline creatinine (mg/dl)	1.20±1.08	1.17±0.98	0.034	1.20±1.08	1.20±0.10	0.000	1.39±1.30	0.159
PCI procedure								
Performed on emergency basis (%)	13.0	18.7	0.158	13.0	12.9	0.004	17.5	0.126
Bivalirudin exposure (%)	67.9	64.4	0.072	67.9	68.7	0.019	67.5	0.008
Left main coronary artery (%)	2.1	2.2	0.009	2.1	2.2	0.005	2.5	0.027
No. of vessels treated during index procedure	1.42±0.71	1.44±0.73	0.024	1.42±0.71	1.42±0.70	0.004	1.78±0.97	0.361
Duration of fluoroscopy (min)	12.5±9.7	14.1±11.2	0.142	12.5±9.2	12.6±8.9	0.009	122.6±72.2	2.140
No. of procedures during admission	1.05±0.22	1.05±0.22	0.002	1.05±0.22	1.05±0.22	0.003	1.03±0.16	0.102

* Plus–minus values are means ±SD. To convert the values for creatinine to micromoles per liter, multiply by 88.4. NSTEMI denotes non–ST-segment elevation myocardial infarction, and PCI percutaneous coronary intervention.
† The standardized difference (i.e., the mean between-group difference divided by the standard deviation) was calculated to assess the relative imbalance between the exposed and unexposed groups, with values of less than 0.100 considered to be adequately balanced. The standardized difference for unmatched exposures compared these patients with those who had received the Mynx device and were included in the propensity matching.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.

The NEW ENGLAND JOURNAL of MEDICINE

Figure 1. Cumulative Incidence of Any Vascular Complication among Recipients of the Mynx Device and Alternative Devices (January 1, 2011–September 30, 2013)



Resnic FS et al. N Engl J Med 2017;376:526-535.

Resnic FS et al. N Engl J Med 2017;376:526-535.

Table 2. Outcomes and Final Alert Status for Propensity-Matched Analysis of Recipients of the Mynx Device and Alternative Devices (January 1, 2011–September 30, 2013).

Cohort	Mynx Device	Alternative Device	Relative Risk (95% CI)	P Value	Absolute Risk Difference*	Time to Alert
	no. of patients (%)				*percentage points*	*mo*
Overall study population						
No. of patients	73,124	73,124				
Vascular complications	883 (1.2)	555 (0.8)	1.59 (1.42–1.78)	<0.001	0.4	9
Access-site bleeding	277 (0.4)	207 (0.3)	1.34 (1.10–1.62)	0.001	0.1	30
Blood transfusion	1,328 (1.8)	1,080 (1.5)	1.23 (1.13–1.34)	<0.001	0.3	15
High-risk subgroup						
Age ≥70 yr						
No. of patients	27,293	27,293				
Vascular complications	447 (1.6)	231 (0.8)	1.94 (1.63–2.29)	<0.001	0.8	9
Access-site bleeding	142 (0.5)	70 (0.3)	2.03 (1.49–2.76)	<0.001	0.3	15
Blood transfusion	754 (2.8)	621 (2.3)	1.21 (1.08–1.36)	<0.001	0.5	27
Diabetes						
No. of patients	29,097	29,097				
Vascular complications	307 (1.1)	178 (0.6)	1.72 (1.42–2.10)	<0.001	0.4	15
Access-site bleeding	101 (0.3)	63 (0.2)	1.60 (1.14–2.25)	0.003	0.1	24
Blood transfusion	634 (2.2)	539 (1.9)	1.18 (1.04–1.33)	0.005	0.3	24
Women						
No. of patients	25,065	25,065				
Vascular complications	544 (2.2)	297 (1.2)	1.83 (1.58–2.13)	<0.001	1.0	9
Access-site bleeding	182 (0.7)	100 (0.4)	1.82 (1.40–2.36)	<0.001	0.3	15
Blood transfusion	795 (3.2)	593 (2.4)	1.34 (1.20–1.50)	<0.001	0.8	15

* The absolute risk difference was calculated as the rate for the Mynx device minus the rate for the alternative devices, with all percentages carried to one decimal place.

The NEW ENGLAND JOURNAL of MEDICINE

Resnic FS et al. N Engl J Med 2017;376:526-535.
With a negative control (Falsification Hypothesis)

Table 3. Outcomes and Final Alert Status in Propensity-Matched Analyses of Mynx High-Use Centers, Signal Persistence, and Falsification Hypothesis.*

Cohort Analyzed	Mynx Device	Alternative Device	Relative Risk (95% CI)	P Value	Absolute Risk Difference	Time to Alert
	no. of patients (%)				*percentage points*	*mo*
Mynx high-use centers						
No. of patients	28,107	28,107				
Vascular complications	297 (1.1)	208 (0.7)	1.43 (1.18–1.73)	<0.001	0.3	12
Access-site bleeding	101 (0.4)	63 (0.2)	1.60 (1.14–2.25)	0.003	0.1	15
Blood transfusion	444 (1.6)	364 (1.3)	1.22 (1.05–1.41)	0.005	0.3	21
Signal persistence†						
No. of patients	48,992	48,992				
Vascular complications	704 (1.4)	472 (1.0)	1.49 (1.32–1.68)	<0.001	0.5	6
Access-site bleeding	355 (0.7)	248 (0.5)	1.43 (1.21–1.69)	<0.001	0.2	12
Blood transfusion	725 (1.5)	614 (1.3)	1.18 (1.06–32)	<0.001	0.2	12
Falsification hypothesis‡						
No. of patients	73,124	73,124				
Contrast-induced nephropathy	2,507 (3.4)	2,384 (3.3)	1.05 (0.99–1.11)	0.07	0.2	NA

* NA denotes not applicable.
† To assess the persistence of the potential safety signal identified in the primary analysis, a further analysis was performed on an additional 49,037 PCI procedures in which the Mynx device was used from April 1, 2014, to September 30, 2015.
‡ A falsification-hypothesis analysis was performed as one of several post hoc sensitivity analyses to assess the robustness of the primary findings. In the falsification-hypothesis analysis, the original matched patient cohorts were evaluated for the development of postprocedural nephropathy that was associated with the use of iodine as a radiographic contrast agent (contrast-induced nephropathy).

PLOS | ONE

RESEARCH ARTICLE

Clinical Outcomes in Low Risk Coronary Artery Disease Patients Treated with Different Limus-Based Drug-Eluting Stents - A Nationwide Retrospective Cohort Study Using Insurance Claims Database

Chao-Lun Lai[1,2,3], Ching-Fen Wu[4], Raymond Nien-Chen Kuo[5,6], Yen-Yun Yang[6], Ming-Fong Chen[7], K. Arnold Chan[8,9], Mei-Shu Lai[3,6]*

1 Department of Internal Medicine and Center for Critical Care Medicine, National Taiwan University Hospital Hsin-Chu Branch, Hsin-Chu, Taiwan, **2** Department of Internal Medicine, College of Medicine, National Taiwan University, Taipei, Taiwan, **3** Institute of Epidemiology and Preventive Medicine, College of Public Health, National Taiwan University, Taipei, Taiwan, **4** Department of Internal Medicine, Mennonite Christian Hospital, Hualien, Taiwan, **5** Institute of Health Policy and Management, College of Public Health, National Taiwan University, Taipei, Taiwan, **6** Center for Comparative Effectiveness Research, National Center of Excellence for Clinical Trial and Research, National Taiwan University Hospital, Taipei, Taiwan, **7** Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan, **8** Department of Medical Research, National Taiwan University Hospital, Taipei, Taiwan, **9** Graduate Institute of Oncology, College of Medicine, National Taiwan University, Taipei, Taiwan

CrossMark
click for updates

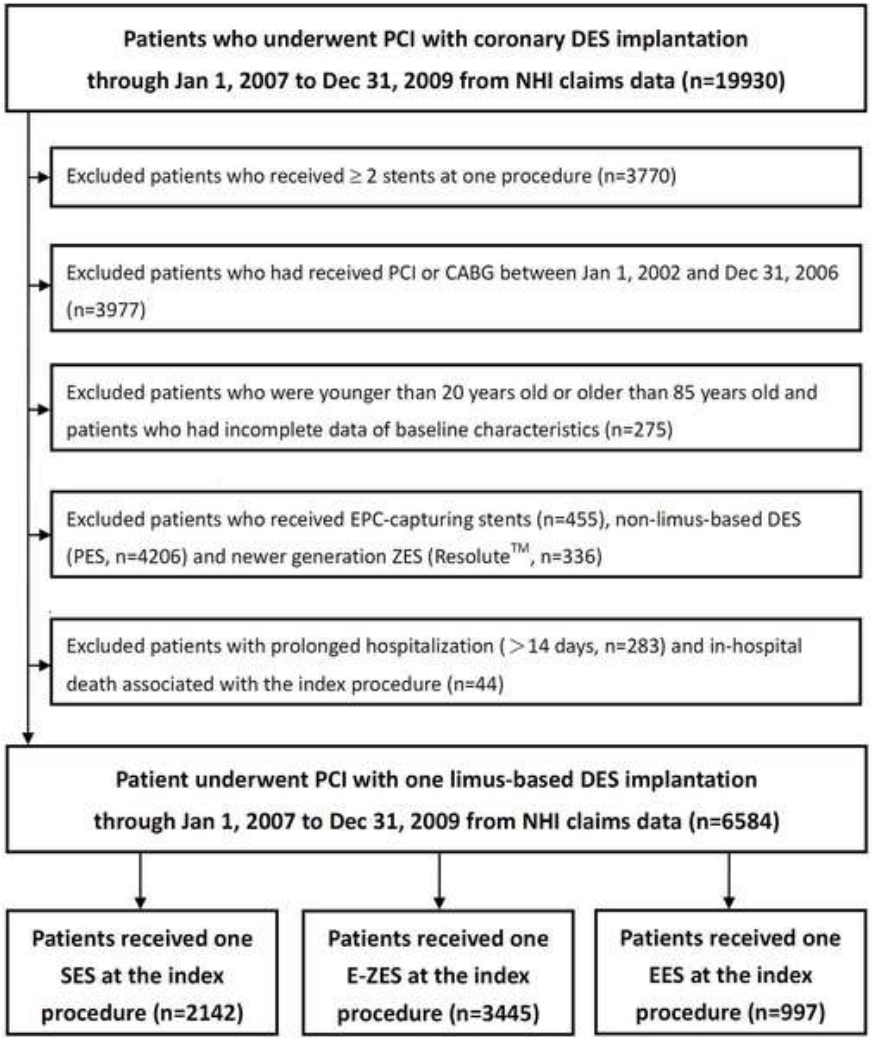
OPEN ACCESS

Citation: Lai C-L, Wu C-F, Kuo RN-C, Yang Y-Y, Chen M-F, Chan KA, et al. (2015) Clinical Outcomes

National Health Insurance claims data in Taiwan

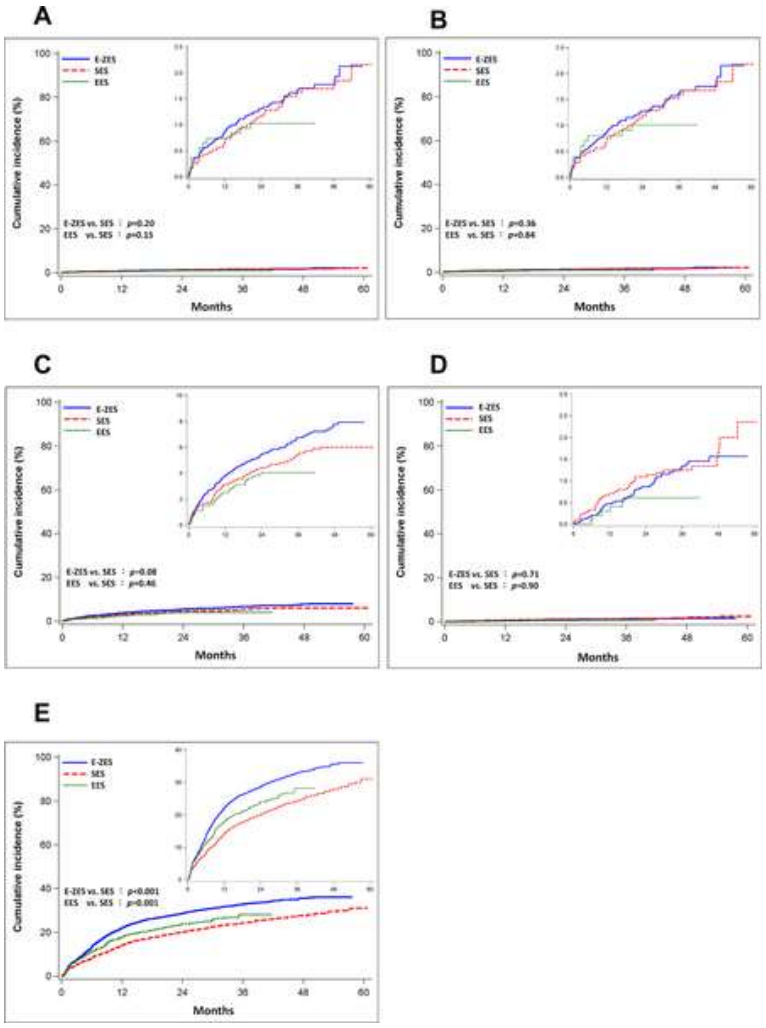
- Single payer, comprehensive coverage (>99%)
  - Population-based
- Limited clinical information
- Could be linked to mortality data and other health data, such as cancer registry

Fig 1. Flow chart of the study.



Lai CL, Wu CF, Kuo RNC, Yang YY, Chen MF, et al. (2015) Clinical Outcomes in Low Risk Coronary Artery Disease Patients Treated with Different Limus-Based Drug-Eluting Stents - A Nationwide Retrospective Cohort Study Using Insurance Claims Database. PLOS ONE 10(4): e0122860. https://doi.org/10.1371/journal.pone.0122860
http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0122860

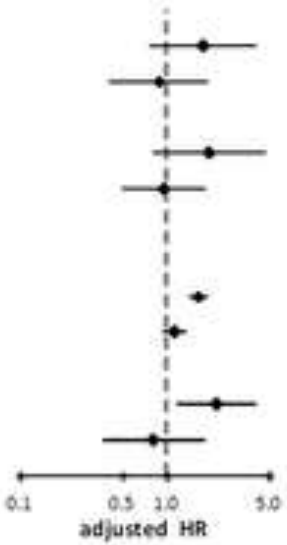
Fig 2. Kaplan-Meier cumulative incidences of different clinical end-points in three stent groups.

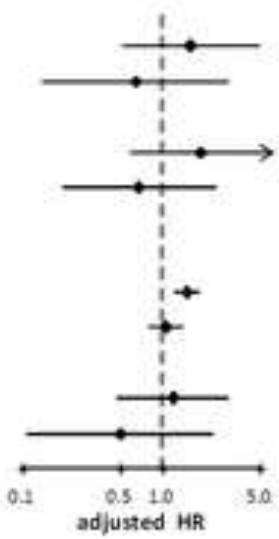


Lai CL, Wu CF, Kuo RNC, Yang YY, Chen MF, et al. (2015) Clinical Outcomes in Low Risk Coronary Artery Disease Patients Treated with Different Limus-Based Drug-Eluting Stents - A Nationwide Retrospective Cohort Study Using Insurance Claims Database. PLOS ONE 10(4): e0122860. https://doi.org/10.1371/journal.pone.0122860 http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0122860

Fig 3. Relative risk of individual clinical end-point in two composite end-points among E-ZES and EES groups.

	E-ZES			EES		
	HR	(95%CI)	p	HR	(95%CI)	p
Composite end-point of acute coronary events						
Acute myocardial infarction						
within 1 year	1.78	(0.78- 4.06)	0.17	1.61	(0.53- 4.94)	0.40
after 1 year	0.89	(0.41- 1.90)	0.75	0.65	(0.14- 2.98)	0.58
Emergency PCI						
within 1 year	1.96	(0.82- 4.68)	0.13	1.89	(0.60- 5.96)	0.28
after 1 year	0.97	(0.51- 1.83)	0.92	0.69	(0.20- 2.41)	0.57
Composite end-point of repeated coronary revascularization						
Repeated PCI						
within 1 year	1.64	(1.43- 1.89)	<0.001	1.51	(1.24- 1.85)	<0.001
after 1 year	1.13	(0.96- 1.33)	0.14	1.08	(0.82- 1.42)	0.59
CABG						
within 1 year	2.20	(1.19- 4.08)	0.012	1.20	(0.48- 3.00)	0.70
after 1 year	0.82	(0.37- 1.81)	0.62	0.51	(0.11- 2.33)	0.38





Lai CL, Wu CF, Kuo RNC, Yang YY, Chen MF, et al. (2015) Clinical Outcomes in Low Risk Coronary Artery Disease Patients Treated with Different Limus-Based Drug-Eluting Stents - A Nationwide Retrospective Cohort Study Using Insurance Claims Database. PLOS ONE 10(4): e0122860. https://doi.org/10.1371/journal.pone.0122860
http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0122860

Environmental Health and Preventive Medicine 2017; 22: 51

STUDY PROTOCOL Open Access

Analysis of the evidence-practice gap to facilitate proper medical care for the elderly: investigation, using databases, of utilization measures for National Database of Health Insurance Claims and Specific Health Checkups of Japan (NDB)

Takeo Nakayama[1*], Yuichi Imanaka[2], Yasushi Okuno[3], Genta Kato[4], Tomohiro Kuroda[5], Rei Goto[6,11], Shiro Tanaka[7], Hiroshi Tamura[5], Shunichi Fukuhara[8], Shingo Fukuma[8], Manabu Muto[9], Motoko Yanagita[10], Yosuke Yamamoto[8] and on behalf of BiDAME: Big Data Analysis of Medical Care for the Elderly in Kyoto

Ongoing collaboration with Kyoto U

- kachan@ntu.edu.tw
- hdrc.ntu.edu.tw