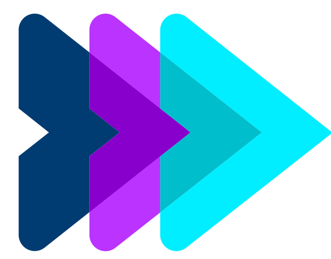

Validating the Clinical Utility of Intravascular Ultrasound Guidance during Lower-Extremity Peripheral Vascular Interventions using Claims Data in Japan from 2009-2020: A Real-World Evidence Study Protocol

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OBJECTIVE

To investigate the long-term clinical effectiveness and costs associated with intravascular ultrasound (IVUS) guidance during lower-extremity peripheral vascular interventions (LE-PVI) in Japan.

BACKGROUND

- LE-PVI is used to treat peripheral artery disease (PAD), which is characterized by stenosis and/or occlusions of the medium to large arteries in the lower-limbs.
- The clinical-utility of IVUS-guidance during LE-PVI to treat PAD via endovascular therapies (balloon angioplasty or stenting) is well-established[1-3].
- Moreover, IVUS-use during LE-PVI was associated with lower incidence of vascular complications and major limb events[3].
- However, there is limited long-term outcomes data among Asian patients undergoing LE-PVI with and without IVUS.
- Widespread-use of IVUS is limited across many Western healthcare settings, due to lack of dedicated reimbursement for IVUS.
- IVUS has been separately and non-discriminatorily reimbursed since 1994 in Japan for coronary and peripheral vascular interventions[4].

METHODS

Study Design

This is a retrospective, comparative effectiveness study using data from the Medical Data Vision (MDV) database in Japan. Two study groups were considered, "IVUS" vs "Angiography-only" based on certain criteria.

Data Source/ Study Population

MDV is a nation-wide health claim database comprising data from 400 partner hospitals, covering all (>100) insurance types in Japan (Social/National/Latter-Stage Elderly Insurance).

Inclusion criteria	Exclusion criteria
• Being at least 18 years old at baseline • Having at least one endovascular procedure code & ICD-10 or disease code for PAD# • Having at least one STM/ medical device label code related to IVUS or angiography#	• Failing to have at least 1 healthcare claim recorded in the 12 months preceding index date* • Having a missing record of angiography or IVUS performed • Having other imaging techniques performed (e.g., OCT)

* To identify baseline characteristics at inclusion

Study Period

Selection period: April 2008 to July 2020 considering the pre-index and follow-up durations required

Inclusion period: April 2009 to July 2020; **Index date:** date of first hospitalization of endovascular interventional procedure associated with a PAD diagnosis occurring within the inclusion period.

Follow-up (FU) period: period starting from the index date (inclusive) until the end of the claims (July 31, 2020), subsequent endovascular procedure, or death (whichever event comes first).

Endpoints

Clinical outcomes identified through MDV, ICD-10-, disease-, procedure codes#		Economic
• Hospital mortality • Major amputation • Stroke • Stent thrombosis • Acute myocardial infarction (AMI)	• Repeat endovascular intervention • **Major adverse cardiac event (MACE):** stroke; AMI or mortality • **Major adverse limb event (MALE):** Major amputation, stent thrombosis or mortality • **Major adverse cardiac or limb event (MACLE):** composite of all events	• **Total costs:** costs related to initial procedure & all follow-up events, including drug costs, from claim records

Statistical Analyses

- **Summary statistics** (mean, median, frequencies) will be used to summarize patient demographics and comorbidities at inclusion, defined as baseline characteristics; and incidence of events & costs.

Baseline characteristics identified through MDV, ICD-10-, disease-, procedure codes#	
• Age (years)	• Stable angina
• Gender	• Chronic obstructive pulmonary disease
• Hypertension	• Cerebrovascular accident
• Hyperlipidemia	• Smoking status
• Insulin-use	• History of amputation
• Chronic kidney disease	• Device type (bare metal stent, drug-eluting stent, drug-coated balloon, balloon angioplasty)
• Acute coronary syndrome	

- **Chi-square test** used to test the significance of difference of incidence of events between the two groups.
- **Time-to-event analyses,** where patients without the event will be censored. Univariate analyses used to identity candidate variables ($p<0.2$) for multivariate analyses from the list of baseline characteristics.

Time-to-event analyses	Output
Kaplan-Meier and Cox proportional hazard model	• Probabilities of being event-free over the follow-up / median time-to-event • Adjusted hazard ratio to determine whether IVUS affects the time-to-event
Cumulative incidence function and cause-specific model, where death was considered a competing risk	

- **Propensity-score matching** analysis used to further validate multivariate analyses by creating two groups with similar baseline characteristics. Propensity-scores generated using a logistic regression model against outcome as IVUS status (yes; or no), including all baseline characteristics. 1:1 Nearest Neighbor matching technique used to randomly select cases & controls with a caliper width less than or equal to 0.2 times pooled standard deviation of the logit of the propensity scores for the cohort.
- **Costs** expressed in person-year to investigate average cost/ patient/ year of FU. Trends in total costs will be measured using summary statistics in the propensity-score matched cohorts.

Cost analyses (pre-matched cohort)	Output
Non-parametric bootstrap analysis using 10,000 samples with replacement	• The mean total cost difference (across 10,000 samples) and the associated 95% confidence interval.
Generalized linear model (Poisson, lognormal or gamma distribution).	• Impact of IVUS guidance on total healthcare costs, adjusting for baseline characteristics, where variables with significance ($p<0.2$) in univariate included in multivariate regression.

- **Sub-group analyses** will be performed according to arterial segment (iliac, femoropopliteal) and severity of disease (critical limb ischemia), identified using ICD-10 diagnostic codes for the index hospitalization#.

CONCLUSIONS

To our knowledge, this is the first large-scale (N=9,845), real-world evidence study performed to validate the long-term clinical utility and costs of IVUS-guidance during LE-PVI among PAD patients in Asia.

LIMITATIONS

- Given this is not a randomized study, selection bias may be present. The impact of confounding bias will be reduced using adjusted regression models. However, it is still possible that some cofounders may exist that cannot be accounted for.
- The available data is dependent on the quality of the information inputted by healthcare professionals, which is a common limitation in studies based on Electronic Medical Records.
- In the MDV dataset, it is not possible to continuously track patients from one institution to another. When a patient changes providers, their unique identifiers change, which may cause them to appear as two or more different patients in the current dataset . However, this is likely to underestimate than overestimate study results. Furthermore, this limitation is likely to be minimal, as we only included those with a continuous history of enrolment with a specific provider (12-month pre-index period).

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\# supplemental material available with poster