Comparing Cardiovascular Outcomes Among Heated Tobacco Product Users, Cigarette Smokers, Former Smokers, and Never Smokers: Protocol for a Real-World Retrospective Study in Japan

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Abstract

Background: Smoking is a known risk factor for cardiovascular diseases (CVD). Despite widespread knowledge of the health risks of combustible cigarettes (CIG), many smokers continue to smoke. There have been efforts to provide alternatives, such as heated tobacco products (HTP), that may be less harmful than CIG.

Objective: To evaluate the impact of switching from CIG to HTP on the time to first subsequent major adverse cardiovascular event (MACE) compared with continued CIG smoking.

Methods: This retrospective cohort study will use health data from the Tokushukai Medical Database and tobacco exposure data from questionnaires and consumer databases in Japan. The study will include patients with a first cardiovascular event of non-fatal myocardial infarction (MI), unstable angina, or urgent coronary revascularization between May 2016 and December 2020 (Index Event); patients will be observed until March 2025. The primary exposure of interest is HTP use, while the primary comparator is continued CIG smoking pre- and post-index. The primary outcome is first post-index MACE (a composite outcome of any of the following: non-fatal MI, non-fatal stroke, hospitalization for angina, hospitalization for heart failure, urgent revascularization for angina, or all-cause mortality). After accounting for potential confounding factors with a propensity score weighting method, weighted log-rank tests and a weighted non-proportional Cox model will be used to compare the primary outcome between the exposure groups. Dual use of CIG and HTP, quitting CIG, and never smoking will also be analyzed as ancillary exposure groups to address secondary objectives.

Results: The study described in this protocol intends to assess whether there is a longer time to first MACE in HTP users as compared to CIG smokers.

Conclusions: This protocol describes a large-scale study that intends to identify patients with CVD from a nationally representative healthcare database and utilizes multiple data sources to evaluate their history of tobacco product usage. This will be the first study to assess the effect of HTP use on CVD outcomes by sex. Given the limited evidence on the health impacts of HTP in relation to CVD, the results of this study will provide insights into the effect of switching to HTP use compared to continued CIG smoking in patients with a prior cardiovascular event.

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Original Manuscript

Original Paper

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Comparing Cardiovascular Outcomes Among Heated Tobacco Product Users, Cigarette Smokers, Former Smokers, and Never Smokers: Protocol for a Real-World Retrospective Study in Japan

Short title: Retrospective study of cardiovascular disease outcomes among HTP users and cigarette smokers

Abstract

Background: Smoking is a known risk factor for cardiovascular diseases (CVD). Despite widespread knowledge of the health risks of combustible cigarettes (CIG), many smokers continue to smoke. There have been efforts to provide alternatives, such as heated tobacco products (HTP), that may be less harmful than CIG.

Objective: To evaluate the impact of switching from CIG to HTP on the time to first subsequent major adverse cardiovascular event (MACE) compared with continued CIG smoking.

Methods: This retrospective cohort study will use health data from the Tokushukai Medical Database and tobacco exposure data from questionnaires and consumer databases in Japan. The study will include patients with a first cardiovascular event of non-fatal myocardial infarction (MI), unstable angina, or urgent coronary revascularization between May 2016 and December 2020 (Index Event); patients will be observed until March 2025. The primary exposure of interest is HTP use, while the primary comparator is continued CIG smoking pre- and post-index. The primary outcome is first post-index MACE (a composite outcome of any of the following: non-fatal MI, non-fatal stroke, hospitalization for angina, hospitalization for heart failure, urgent revascularization for angina, or all-cause mortality). After accounting for potential confounding factors with a propensity score weighting method, weighted log-rank tests and a weighted non-proportional Cox model will be used to compare the primary outcome between the exposure groups. Dual use of CIG and HTP, quitting CIG, and never smoking will also be analyzed as ancillary exposure groups to address secondary objectives.

Results: The study described in this protocol intends to assess whether there is a longer time to first MACE in HTP users as compared to CIG smokers.

Conclusions: This protocol describes a large-scale study that intends to identify patients with CVD from a nationally representative healthcare database and utilizes multiple data sources to evaluate their history of tobacco product usage. This will be the first study to assess the effect of HTP use on CVD outcomes by sex. Given the limited evidence on the health impacts of HTP in relation to CVD, the results of this study will provide insights into the effect of switching to HTP use compared to continued CIG smoking in patients with a prior cardiovascular event.

Keywords: Cardiovascular Diseases; Smokers; Japan; Proportional Hazards Models; Retrospective Studies; Myocardial Infarction; Risk Factors; Stroke

Introduction

Cardiovascular diseases (CVD) are the leading cause of morbidity and mortality in Japan. The age-adjusted incidence rate (per 100,000 population) of myocardial infarction (MI) was 24.4 in 2020 [1, 2] and the mortality rate was 24.9 in 2021 [3]. Given that over 80% of the risks of CVD burden could be attributable to known modifiable risk factors such as cigarette smoking, hyperlipidemia, and obesity, such risks could be significantly reduced through lifestyle modifications [4]. Cigarette smoking as a known major risk factor for CVD [5] is associated with increased mortality [6, 7]. The most effective way for smokers to reduce their risk of CVD is to quit smoking [8-10]. Despite the known health risks associated with smoking, many people continue to smoke. Even though the prevalence of smoking has decreased substantially over the past two decades in the world (from ~33% in 2000 to ~20% in 2022), the World Health Organization (WHO) reported that there were approximately 1.245 billion current tobacco users in the world in 2022 [11]. The WHO has projected this number to decrease only slightly to about 1.197 billion by 2030.

The concept of tobacco harm reduction posits that switching to non-combustible tobacco or nicotine-containing products could reduce the risk of developing smoking-related diseases [12, 13]. Heated tobacco products (HTP), which heat tobacco without burning it to produce aerosols for inhalation [14], are an example of such alternative tobacco products. This viewpoint is supported by aerosol chemistry analyses, which showed substantial reductions in the levels of harmful and potentially harmful constituents in HTP aerosols compared to combustible cigarette (CIG) smoke [15-17]. Additionally, biomarker studies showed that switching to an HTP, compared to continued CIG smoking, led to significantly reduced levels of biomarkers of exposure [18-20] and favorable changes in biomarkers of potential harm [18, 21-24].

Despite these findings and the widespread use of HTP in countries like Japan (with a national prevalence of HTP use of about 12% in 2022) [25], there is a lack of real-world studies assessing the impact of HTP use (vs. CIG smoking and smoking cessation) on CVD outcomes, with only one available real-world study with published results [26]. This study was conducted in a cohort of 5 million South Korean adult males and estimated the risk of CVD among individuals who continued with CIG smoking compared to those who switched to any form of non-combustible nicotine or tobacco products (NNTP), which included HTP and nicotine vaping products (e.g., e-cigarettes). The study reported a lower risk of CVD in recent (< 5 years) NNTP switchers (hazard ratio [HR]: 0.77, 95% confidence interval [CI]: 0.65-0.91) and long-term (≥ 5 years) NNTP switchers (HR: 0.77, 95% CI: 0.58-1.00) when compared to continued CIG smokers. However, interpretation of these findings cannot be generalized to females. Moreover, the number of CVD cases for NNTPs was low – 139 for recent NNTP switchers (0.35%) and 52 for long-term NNTP switchers (0.41%). Furthermore, despite known differences between the delivery mechanisms of the products, results were not analyzed separately for users of HTP and nicotine vaping products.

There is a lack of evidence on the impact of HTP use on CVD outcomes. Given that many patients with CVD are CIG smokers, and about 21% of deaths related to ischemic heart disease have been attributed to CIG smoking [9], assessment of CVD outcomes among CIG smokers who switch to HTP use is essential, especially considering their growing popularity among smokers. This study intends to assess the relative impact of switching to HTP use compared to continued CIG smoking on the further development of major adverse cardiovascular events (MACE) in patients who already survived a CVD event. The study will use a nationally representative Japanese health database to identify patients for study inclusion and assessment of study outcomes. The choice of database is expected to generate a cohort with a large sample size, with approximately 50,000 patients anticipated to be potentially eligible for study inclusion. This will likely help improve the precision and relevance of the study results. Multiple data sources will be used for the assessment of data on tobacco product usage patterns in the study population. Evaluation of the primary study outcome will

be based on a composite 6-point MACE, which will likely increase the number of outcome events for risk estimation. Furthermore, individual cardiovascular events will be analyzed as secondary outcomes to address additional study objectives. Overall, the results from this study will likely address some of the existing knowledge gaps and provide additional real-world evidence on the risk profile of HTP use relative to CIG smoking, dual use of HTP and CIG, quitting smoking, and never smoking in CVD patients.

Study Objectives

Primary Objective

The primary objective is to compare the time from a patient's Index Event to the first post-index MACE between comparable groups of HTP users and CIG smokers. An Index Event is defined as the first record of any of the following: non-fatal MI, unstable angina, or urgent coronary revascularization procedure, between May 1, 2016 and December 31, 2020. The primary study outcome is a "Broad Modified MACE" [27], which is a 6-point composite outcome consisting of any of the following:

- Nonfatal MI
- Nonfatal stroke
- Hospitalization for angina
- Hospitalization for heart failure
- Urgent revascularization for angina, or
- All-cause mortality

Secondary Objectives

The secondary objectives are to evaluate further study outcomes among patients with different patterns of tobacco product use:

- To compare the time from the Index Event to all-cause mortality between comparable groups of:
  i) HTP users versus CIG smokers,
  ii) HTP users versus dual users of CIG and HTP (hereafter, dual users. See Table 1 for definition),
  iii) HTP users versus former smokers, and
  iv) HTP users versus never smokers
- To compare the time from the Index Event to the Broad Modified MACE between comparable groups of:
  i) HTP users versus former smokers,
  ii) HTP users versus dual users, and
  iii) HTP users versus never smokers
- To compare the frequency of post-index CVD-related hospitalizations (defined as hospitalizations due to MI, unstable angina, or stroke) by exposure groups (never smokers, former smokers, dual users, CIG smokers, and HTP users)
- To evaluate whether the time from the Index Event to a first post-index Broad Modified MACE (if occurring) for HTP users versus CIG smokers varies for HTP users by:
  i) The total number of years of HTP use (ie, regardless of Index Event)
  ii) Age at Index Event
  iii) Sex
  iv) History of CVD prior to the Index Event (e.g., stroke, hypertension, peripheral vascular disease [PVD])

Table 1. Tobacco exposure groups and definitions.

CIG smokers	HTP users	Dual users of CIG and HTP	Former smokers	Never smokers
• Smoked ≥ 1 CIG daily *AND* • Did not use HTP or used HTP consumables less than daily	• Used ≥ 1 HTP consumable daily *AND* • Did not smoke CIG or smoked less than daily	• Smoked ≥ 1 CIG daily *AND* • Used ≥ 1 HTP consumable daily	• Did not use any tobacco product *AND* • Smoked ≥ 100 CIG in the lifetime or smoked ≥ 1 CIG daily for at least 1 year prior to the Index Event	• Has either never smoked CIG or had smoked < 100 CIG in their lifetime up to the primary outcome event or censoring

CIG, combustible cigarette; HTP, heated tobacco product.

Methods

Study Design

This retrospective cohort study aims to assess the association between patients' tobacco use habits and the risk of MACE in a cohort of Japanese patients with a history of non-fatal MI, unstable angina, or an urgent coronary revascularization procedure (**Appendix I**). The study will be conducted using the Tokushukai Medical Group Database (TMG), which is a real-world healthcare database consisting of patients who have sought medical care at a hospital that is part of the Tokushukai Medical Corporation, a healthcare network of about 75 hospitals in Japan. Questionnaires completed by patients or their relatives will be used to obtain information on tobacco exposure history. In addition, consumer data on the purchase history of tobacco products will be obtained and linked with patient information to enable further assessment of tobacco product use patterns, where applicable. The study protocol, informed consent form (ICF), enrollment outreach materials, and questionnaires were reviewed and approved by the Tokushukai Group's Ethics Committee (approval number: TGE02549-008).

Figure 1 provides an overview of the study design and conduct. Patients in the TMG who have a record of an Index Event between May 1, 2016 and December 31, 2020 will be identified and pre-screened for study eligibility. Those who are considered potentially eligible will be sent a study invitation package via postal mail using their personally identifiable information recorded in the TMG (PII; eg, name, address, etc.). If there is no reply to the initial outreach, another attempt will be made within 3 weeks of initial contact. In the study invitation package, there will be an ICF, a data request form (DRF; for querying and linking across data sources), a Tobacco Exposure Questionnaire (TEQ) for patients, and a Relatives' Questionnaire (RQ) for patients' relatives. If patients are deceased or are unable to provide consent on their own, any of their relatives or legal guardian, as the case may be, can participate in the study on behalf of the patient and return the signed ICF and DRF and complete the RQ. Relatives do not need to return the TEQ, as it is designed for patients to complete. Relatives will complete the RQ, which contains questions for proxy assessment of the patient's tobacco exposure history and provision of mortality information in case the patient is deceased.

Upon data collection and prior to merging the tobacco exposure and healthcare data for the analysis of the study objectives, two separate raw datasets will be created for the purpose of conducting a data

check on exposure history and events. The results of the data checks will inform the patterns of tobacco product use and the number of events of the overall study cohort, and will help orient the main study analysis [28].

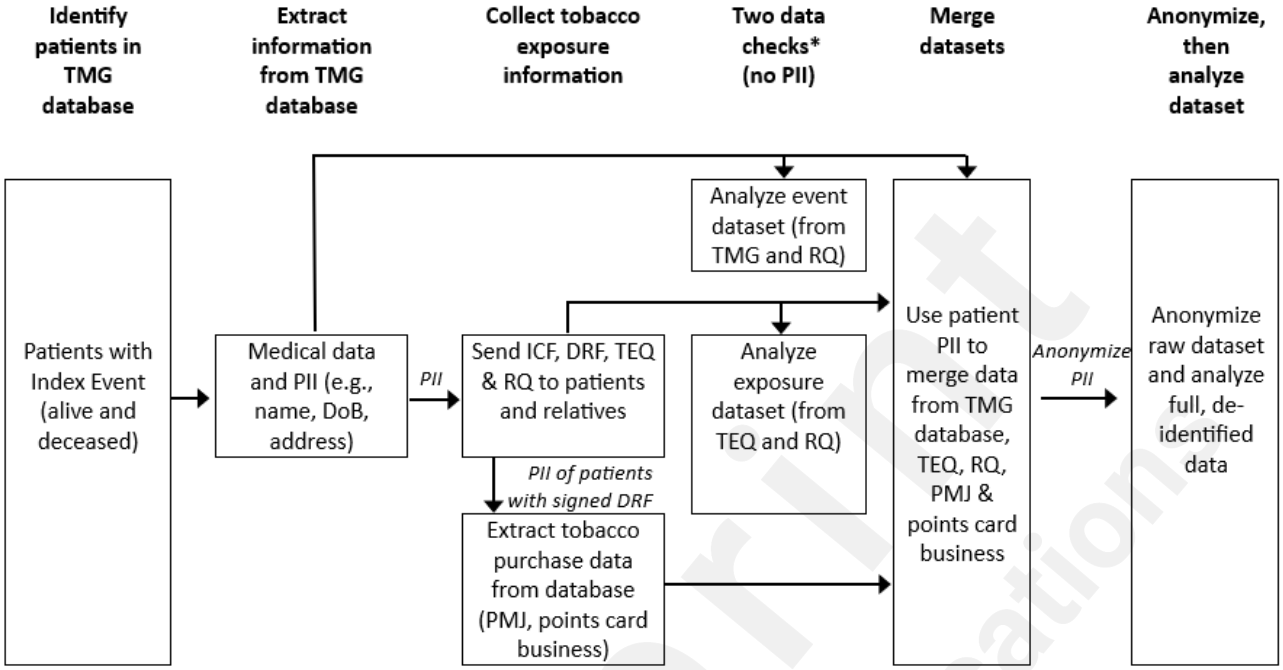

Figure 1. Overview of study design and data flow.

DoB, date of birth; DRF, data request form for permission to access consumption data; ICF, informed consent form; PMJ, Philip Morris Japan; PII, personally identifiable information (eg, combination of full name, date of birth, and address); RQ, Relatives' Questionnaire (to be completed by relatives of deceased and alive patients [those unable to complete the questionnaire themselves] to collect tobacco exposure and mortality data); TEQ, Tobacco Exposure Questionnaire; TMG, Tokushukai Medical Group.

*Data checks will be performed using data of patients whose ICF has been signed.

Figure 2 provides an overview of the relationships between the eligibility assessment, cohort entry, and exposure (tobacco use) and outcome assessment time windows. The date of the Index Event will be the patient's cohort entry date. Study inclusion eligibility for each patient will be assessed based on medical data available prior to the respective cohort entry date. Study outcomes will be assessed during the follow-up period, which starts from the cohort entry date (i.e., Index Event), while tobacco exposure status will be assessed pre- and post-index until the end of the study follow-up period (March 31, 2025).

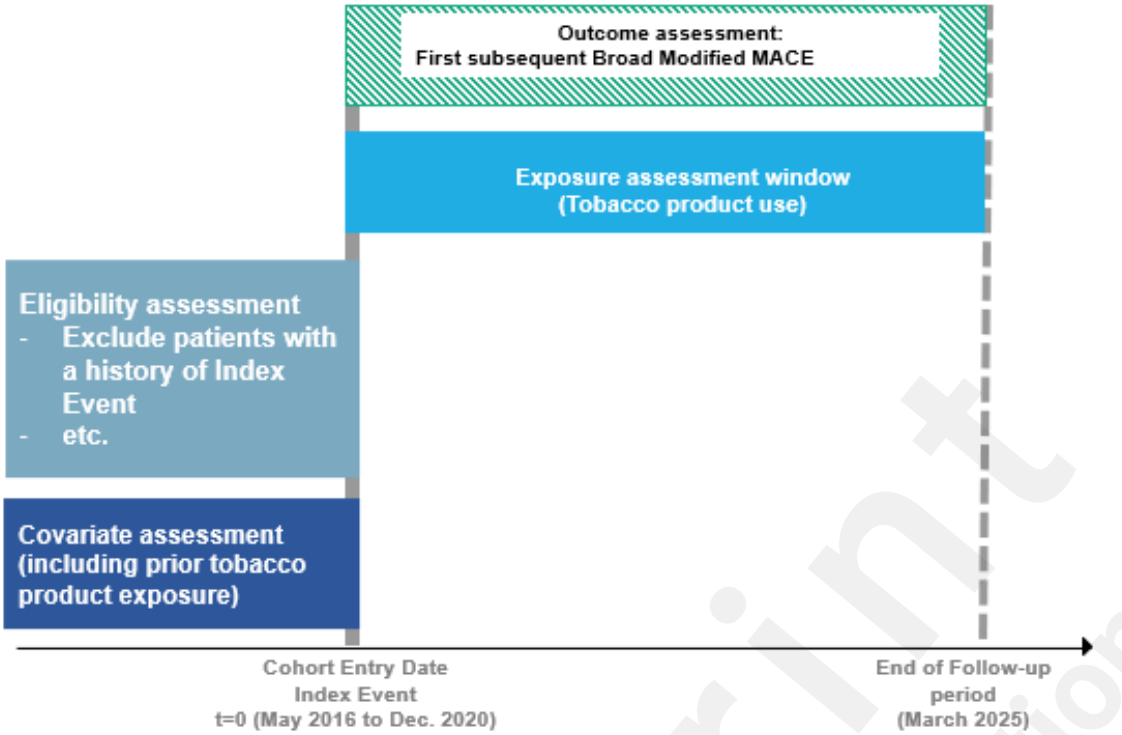

Figure 2. Study period overview. Note: The start of the exposure assessment window (here at Index Event) is illustrative and will be determined after data checks on exposure and events.
MACE, major adverse cardiovascular event.

Participants and Setting

The observational period for this study will be from May 1, 2016 (corresponding to the national availability of HTP in Japan) to March 31, 2025. Based on feasibility counts within the TMG, approximately 50,000 patients could be eligible for this study. The study cohort will consist of patients identified in the TMG who meet all the following inclusion criteria and none of the exclusion criteria (**Table 2**).

Table 2. Study eligibility criteria

Inclusion criteria	• Patients with any healthcare encounter records in the TMG • Patients with first record of the Index Event from May 1, 2016 to December 31, 2020) • Age 30 years or older at the time of the Index Event • Patients of any sex • Patients or relatives who understand the information provided in the ICF and have signed it
Exclusion criteria	• Tobacco industry employees or their first-degree relatives • Employees of the study sponsor and its affiliates or other organizations involved in the study

ICF, informed consent form; TMG, Tokushukai Medical Group Database.

Data Sources and Collection

Several data sources will be used for the conduct of this study:

1. TMG: Electronic medical records from this database will be used to provide health and related data for patient identification, assessment of cohort entry eligibility, and assessment of study outcomes and covariates.
2. Questionnaires: Patients will complete a modified version of the About TEQ (which is part of the ABOUT-Toolbox™) designed specifically for this study for the assessment of tobacco exposure [29]. Relatives responding to the invitation on behalf of patients (alive or deceased) will complete the RQ for the assessment of tobacco exposure and provision of mortality information for deaths that occurred outside of the Tokushukai hospital network (if applicable).
3. Consumer databases (**Appendix II**): Classification of tobacco exposure group (**Table 1**) will be based on patient-/relative-reported information on consumption. Additionally, data will be obtained from the Philip Morris Japan *IQOS*® Database and other Japanese consumer points card business databases. The DRF completed by patients/relatives will provide consent to access patients' purchase history of tobacco products. This data, whenever available, will be reviewed together with the individual's self-reported exposure to tobacco products (information in the TEQ will take priority). The proportion of the study population with information in these databases and the level of concordance between the questionnaires and databases will be presented as study results.

Variables

Tobacco Exposure Definition

Patients will be divided into five mutually exclusive groups based on their assumed tobacco exposure (daily average) between the pre-index period and the end of follow-up (**Table 1**).

Patient assignment into the various exposure groups will depend on their product usage pattern during the exposure assessment window. Notably, a data check will be performed using an exposure dataset that consists of data on tobacco exposure history from the TEQ or RQ and the index date for each patient. The aim of the exposure data check is to assess the persistence on (ie, duration of use of) each type of product use (CIG, HTP, dual use, former use, and no use) [28]. The exposure dataset will not contain any information on health outcomes.

A patient's follow-up time will be censored at the (i) time of a change in tobacco usage pattern

during the follow-up period (eg, changing from one exposure category to another according to the definitions in **Table 2**), (ii) occurrence of an outcome, (iii) exit from the TMG, or (iv) end of the follow-up period. **Figures 3 and 4** provide an illustration of tobacco product exposure for eight hypothetical patients during their follow-up period: **Figure 3** presents how exposure data will be captured, and **Figure 4** presents how an exposure group will be assigned for data analysis.

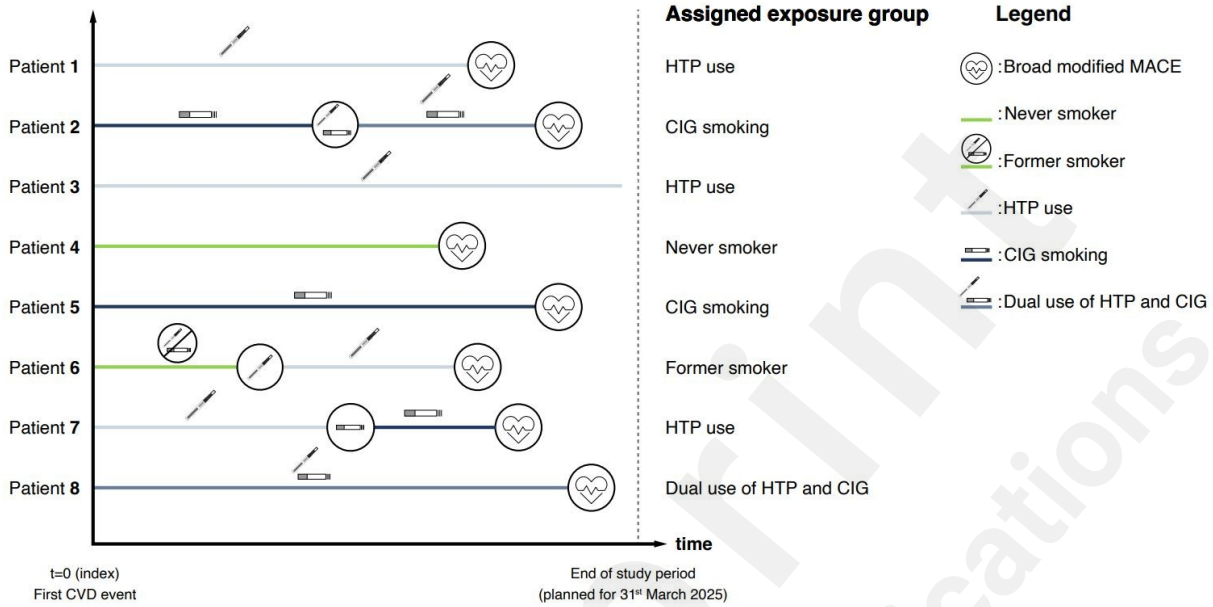

Figure 3

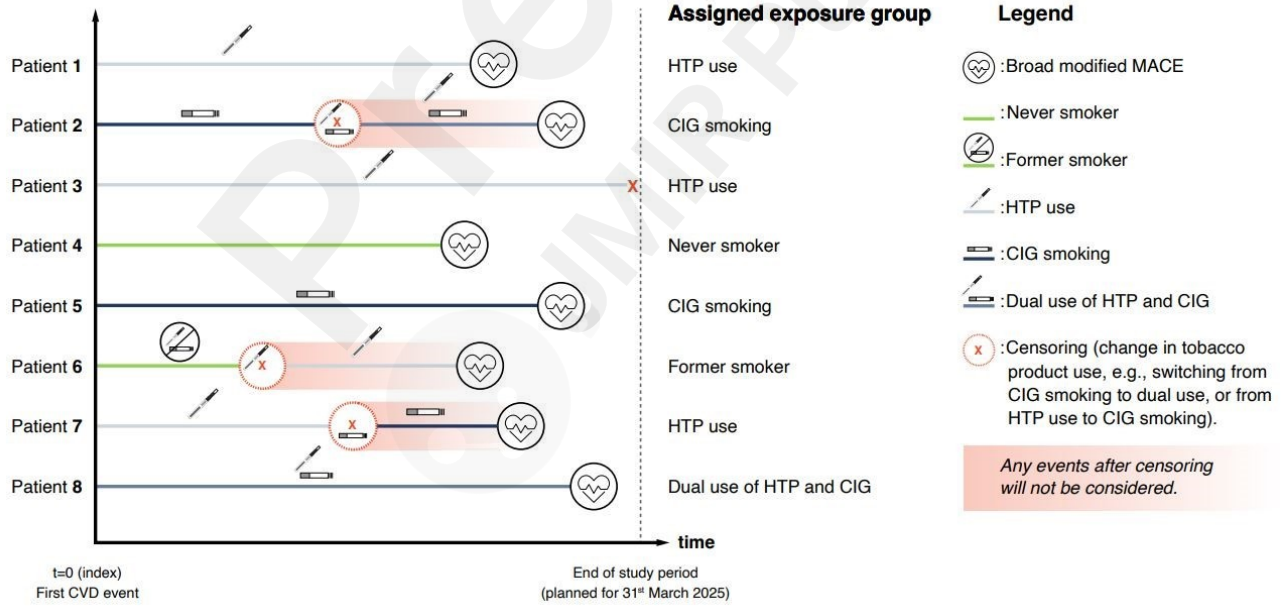

Figure 4

Figures 3 and 4. Classification of patients into exposure groups. Classification will happen before exploring associations with outcomes: (**Figure 3**) Exposure data expected to be collected, (**Figure 4**) Exposure data used to classify patients into exposure groups. The symbol ‘X’ in the figure represents patient censoring at the end of study period, and a circle with a product inside signifies a switch to use of that product. Note: The start of the exposure assessment window (here at index) is illustrative

and will be determined after data checks on exposure and events.
CIG, combustible cigarette; CVD, cardiovascular disease; HTP, heated tobacco product; MACE, major adverse cardiovascular event.

Outcome Definition

Primary Outcome

The primary study outcome is Broad Modified MACE, which is a 6-point composite outcome (individual outcomes listed in the study objectives). The study outcomes will be identified in the TMG using the International Classification of Diseases, Tenth Revision (ICD-10) [30]codes and K-codes for identification of medical and surgical procedures in Japan.
Aside from all-cause mortality, events occurring within 24 hours of the Index Event or within the period of hospitalization (if information is available) due to the Index Event will not be considered as study outcome events, as they might be related to the Index Event. In such cases, the initial event will be considered as the Index Event.
A data check will be performed using an event dataset that consists of health outcomes data obtained from the TMG and RQ (for mortality information). The aim of the event data check is to assess the number of outcome events, drivers of the composite outcome, and time between index date and outcome event [28]. The event dataset will not contain any information on tobacco exposure.

Secondary Outcomes

To address the secondary objectives, time to Broad Modified MACE will be assessed in HTP users compared to former smokers, dual users, and never smokers. In addition, all-cause mortality will be assessed as an individual outcome and compared between HTP users and the other exposure groups. CVD-related hospitalization will be assessed as a secondary outcome and will be identified using the relevant ICD-10 codes (listed in **Appendix III**).

Covariates

Patients' medical records will be accessed from the TMG, and the extracted information will include demographics and medical history vaccine information. A list of some of the relevant covariates and comorbidities can be found in **Appendices IV** and **V**.

Sample Size

The minimum sample size required for the analysis of the primary objective is 5,490 (3,360 CIG smokers and 1,830 HTP users) and 1,590 events. This sample size estimation accounted for 10% of the sample having missing data (on exposure, covariates, and outcomes) and propensity score weighting of data (inflation by 30%). A larger sample size may be required for the secondary objectives. However, this study will be statistically powered if the number of events is met, regardless of the minimum sample size required. In case the number of events identified is insufficient, the study will be conducted but reconsidered as exploratory.
The sample size estimation was calculated based on estimates obtained from the published literature. We assumed the ratio of current CIG smokers to current HTP users to be 2:1 based on a 2020 study in Japan that found a prevalence of 25.9% for CIG smoking and 10.9% for HTP use [31]. A meta-analysis found the yearly proportion of a 3-point MACE (subsequent MI diagnosis, subsequent stroke diagnosis, and cardiovascular mortality) to be 7% among patients who continued CIG smoking [10], and this yearly proportion of MACE was used to calculate the sample size for the primary objective. The average follow-up duration of the studies included in the meta-analysis was 5.4 years. The observational period for this study will be from May 1, 2016 to March 31, 2025, with the latest possible Index Date being in December 2020. Therefore, the minimum follow-up period will be about 4 years for patients without an observed outcome or who were not censored during their follow-up period. The maximum follow-up will be 8 years and 11 months. Based on this, an

average follow-up period of 5 years is assumed for this study. A non-proportional HR was assumed in the sample size calculation to account for the delayed effect of a decrease in risk of a CVD event in HTP switchers due to the accumulated years of previous smoking compared to continued CIG smokers. The yearly HR for patients that switched to HTP (vs. continued CIG smoking) was estimated based on a population modeling study for stroke [32]. The assumptions used for the sample size calculation are summarized in **Appendix VI**.

Data protection and privacy

Throughout the conduct of the study, only Tokushukai Information System, the data management department for the TMG, will have access to patients' PII. After data collection and the exposure and event data checks, a contract research organization (CRO) managing the study will use patient' identification number (a pseudonymized patients' number created by the Tokushukai Information System) to merge the tobacco exposure data (from TEQ, RQ, and consumer databases) and healthcare data (from TMG). The CRO will anonymize the merged dataset following local data protection regulations and the General Data Protection Regulation and use the anonymized data for analysis. The study sponsor will not have access to patients' PII and will receive anonymized data only.

Statistical Analysis

Descriptive statistics will be performed to summarize the distribution of sociodemographic characteristics (eg, sex), lifestyle factors (eg, body mass index), and clinical characteristics (eg, history of diabetes) between the five exposure groups. Continuous variables will be summarized using mean and standard deviations, while categorical variables will be summarized using frequencies and percentages.

Methods of Analysis

For the evaluation of post-index Broad Modified MACE, survival curves will be used to report on the time from Index Event to any first Broad Modified MACE for each of the five exposure groups. The study hypothesis under the primary objective (the average time to develop first Broad Modified MACE would be longer in HTP users than in CIG smokers) will be evaluated by one-sided statistical testing and a significance level of 2.5%. All other statistical tests will be two-sided, with a significance level of 5%, unless otherwise specified.

The analysis of the primary outcome will be based on two models: the weighted log-rank test and the weighted non-proportional Cox model. A weighted log-rank test will be used to derive a *P* value to assess the statistically significant difference in time from Index Event to first Broad Modified MACE between HTP users and CIG smokers (reference group). The effect size will be estimated using HRs and 95% CIs via a weighted non-proportional Cox model, which will be based on three principles:

- Restriction of the study population to the time period when their respective tobacco product use remains the same as that at the Index Event (in cases where the patient has a change in tobacco product use, the follow-up time will be censored at the time of change in tobacco product use).
- Use of weighted observations calculated based on propensity score weighting.
- Addition of an interaction term to the model between the tobacco exposure group variable and the logarithm of follow-up time [33]. This interaction term will account for the expected non-proportional hazard assumption due to the delayed effect of a decrease in risk of a Broad Modified MACE in HTP switchers due to the accumulated years of previous smoking compared to continued CIG smokers.

The secondary objectives related to the analysis of time from Index Event to the secondary outcomes will be performed using the same analysis strategy as for the primary outcome. For the analysis of

number and frequency of first CVD-related hospitalizations, annual numbers and frequencies will be calculated for the five exposure groups. The Fine-Gray model, with an interaction term for follow-up time to account for non-proportional hazard and death as a competing event, will be used to analyze the objective [34]. The incidence rate ratio and 95% CIs will be calculated.

It is important to note that the statistical approach will not be restricted to censoring of patients at the time of a change in tobacco product usage pattern during the follow-up period. Other approaches will be explored, e.g., different exposure assessment windows, marginal structural models using time-varying exposure after Index Event.

Plans for Addressing Confounding

For the primary outcome, a propensity score weighting method will be applied to balance potential confounding factors between the tobacco exposure groups (CIG smokers will be the reference group). The following list of factors may be considered as confounders, if available, and included in the propensity score weighting: age, sex, income, year of Index Event, type of Index Event, family history of CVD, source of tobacco exposure data (patient or relative), pack-years of smoking, body mass index, and history of other diseases prior to Index Event – CVD (eg, stroke, hypertension, PVD), dyslipidemia, diabetes, gout, hyperuricemia, chronic obstructive pulmonary disease (COPD), and cancer.

Missing Data

For missing data, the pattern of missingness will be analyzed, and the characteristics of participants with and without missing data will be compared. For variables with a large proportion of missing data (ie, ≥ 30% of the study sample defined *a priori*), imputations for missing data will be considered. However, variables with more than 50% missing data (defined *a priori*) will be removed entirely from the statistical model.

Results

Data collection is anticipated to be completed in the second quarter of 2025. Data quality review and statistical analyses should commence in the third quarter of 2025 and results are expected to be published in 2026.

Discussion

This is a protocol for a large, retrospective, cohort study investigating the effects of switching from CIG smoking to HTP use compared to continued CIG smoking, dual use, quitting CIG, and never smoking on the time to developing further CVD outcomes in patients who had previously experienced a non-fatal MI, unstable angina, or urgent coronary revascularization procedure. Given that CVD is the leading cause of mortality worldwide and CIG smoking is considered one of its major risk factors, the results from this study might be of relevance to adult CIG smokers who seek potentially less harmful alternatives as well as to public health decision makers looking to reduce CVD burden.

Strengths of the Study

A Broad Modified MACE is adopted as the primary study outcome to enhance the sensitivity of the study outcome and increase precision, enabling better detection of potential effects associated with exposure. It encompasses the multiple outcomes suggested by the United States Food and Drug Administration and the European Medical Agency, as well as other important predictors of cardiovascular morbidity. In addition, some of these CVD outcomes will also be assessed (individually or collectively) in the secondary analyses, providing further insights into whether the

composite outcome was predominantly influenced by specific outcomes.

The use of an existing real-world healthcare database is considered another major strength of the study design. The TMG contains information from approximately 75 hospitals and over 13 million patients [35], and the expected large study cohort that can be formed leveraging the TMG should help improve the precision of the results. The inclusion of both males and females in the study cohort and the plan to perform a subgroup analysis based on sex will help to address the shortfall in the analysis of the study by Choi et al. [26] that only included adult males. Thus, the results expected from this study will be more generalizable, and the subgroup analysis will provide information on whether the risk is affected by sex.

Furthermore, the switch from CIG to HTP might affect the proportionality in risk between both groups over time. It is anticipated that the HR may not always be proportional due to the delayed effect of a decrease in risks of CVD events in HTP switchers due to the years of prior smoking compared to continued CIG smokers. The use of a non-proportional hazard model will address this issue.

In addition, this study's use of electronic medical records to objectively determine the study outcome might help prevent biases that might occur if the outcome definition is dependent on patient self-recall. The tobacco exposure information provided by the patients will also have some level of verification using consumer databases, which will prevent reliance on self-reports alone.

Finally, leveraging the use of an existing large healthcare network database will enable us to reach out to approximately 50,000 patients for study inclusion. Merging the anticipated self-report tobacco exposure data and consumer data on purchases of tobacco products have the potential to create a unique dataset to assess the concordance between the different data sources. The opportunity to compare data on tobacco product purchases versus consumption can inform the design of future studies on the utilities of these real-world data sources.

Limitations of the Study

Although the purpose of using a 6-point Broad Modified MACE as the primary outcome is to enhance the sensitivity of the study, it might also lead to the masking of effect for some individual outcomes, where the effect estimate is predominantly driven by one or two outcomes appearing with increased frequency. A few of these outcomes are assessed separately in the secondary objectives. Furthermore, because this study estimates the risk of a CVD event in patients who have already had a CVD event, any expected effect due to switching from CIG to HTP might be attenuated. However, it is expected that the study findings will still be of use to this population, as there generally remains a high risk of MACE occurrence in people with a prior event. For instance, the excess risk of a CVD event for smokers who quit CIG was found to decrease over time, with Lee et al. (2012) reporting that this risk is reduced to half of that for continuing CIG use after 4.4 years (95% CI 3.26 to 5.95 years) [36].

Another limitation is the study's reliance on questionnaires for exposure definition, as this is dependent on patients' and relatives' recollections, which can be subject to bias. This limitation is mitigated to some degree by using consumer databases, which provide data for verification of the questionnaires on the purchase of tobacco products that can be assessed as a proxy for consumption. However, consumer data may not be available for every patient.

Another study limitation is the potential underestimation of mortality due to uncaptured cases occurring outside the Tokushukai institutions (as the TMG mostly captures in-patient mortality within their hospital network). The retrieval of a patient's survival status from relatives might mitigate this; however, this approach will only be applicable to relatives who shared the same mailing address with the patient and have not moved. Also, in cases where a patient visits a hospital outside the Tokushukai network, other subsequent events may be missed. Reverse causality is another potential bias, as CIG smokers with a higher risk of adverse health outcomes may be more likely to switch to HTP use. This concern is addressed as a secondary objective by analyzing total

years of HTP use regardless of the Index Date. Finally, due to the observational nature of the study, the results might be affected by confounding. Our use of propensity score weighting to balance potential confounders may minimize this, but residual confounding due to unmeasured (eg, genetic disposition, dietary changes) or poorly defined confounders remains a concern.

Conclusion

This protocol describes a study that aims to provide valuable real-world evidence on cardiovascular outcomes upon switching to HTP use compared to continued CIG smoking in patients with CVD. The study will include patients with long-term follow-up durations (potentially up to 9 years) using a very large, nationally representative cohort. Considering that the long-term effects of HTP use are still being investigated, data resulting from this study will contribute to the understanding of the effect of switching from CIG smoking to HTP use on CVD outcomes. Additionally, this study protocol is the first in the tobacco medical literature utilizing real-world data on HTP use coming from various sources in a multimodal approach. This embraces multiple data sources related to tobacco exposure, including information on tobacco purchases from consumer databases and questionnaires on tobacco usage to next of kin, caregivers, or relatives. Finally, this study design includes a detailed assessment of the effects of HTP use compared to continued CIG smoking, dual use, quitting CIG, and never smoking on CVD outcomes, employing specific statistical methods to analyze health outcomes following a first cardiovascular event while also addressing and minimizing potential sources of bias.
Furthermore, findings resulting from this study design may help shape physician recommendations as well as patient expectations associated with HTP use and CVD. The study results may also provide evidence to support public health practices and can serve as building blocks to support further studies on HTP use and associated health outcomes.

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Declarations of Interest

Ethics approval and consent to participate

The study was approved by the Tokushukai Group's Ethics Committee, Japan, under the tracking number TGE02549-008.

Consent for publication

Not applicable

Availability of data and materials

Not applicable for study protocols.

Competing interests

HK, AL, DB, PP, BC, and MHaidar are employees of Philip Morris Products S.A. BC, PP, and Mhaidar hold stock in Philip Morris International. HK previously worked for Novartis Pharma A.G. and receives fees for her duties as the Editor-in-Chief of Epidemiologic Methods, a De Gruyter journal. MHaidar previously worked for Kantar Health. BC and MHibino are clinical trial investigators. MHibino is employed by Shonan Fujisawa Tokushukai Hospital and has received speaker fees from Chugai Pharmaceutical Co. Ltd, Ono Pharmaceutical, AstraZeneca, MSD-Merck, and Eli Lilly. SH is employed by Tokushukai Medical Corporation. PP previously worked for Vectura Fertin Pharma. DB was previously employed by the University of the West of Scotland.

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Authors' contributions

All authors equally contributed to the manuscript draft, review, and final approval.

Abbreviations

CI: confidence interval
CIG: combustible cigarettes
COPD: chronic obstructive pulmonary disease
CRO: contract research organization
CVD: cardiovascular diseases
DoB: date of birth
DRF: data request form
HR: hazard ratio
HTP: heated tobacco products
ICD-10: International Classification of Diseases, Tenth Revision
ICF: informed consent form
MACE: major adverse cardiovascular event
MI: myocardial infarction
NNTP: non-combustible nicotine or tobacco products
PII: personally identifiable information
PMJ: Philip Morris Japan
PVD: peripheral vascular disease
RQ: Relatives' Questionnaire
TEQ: Tobacco Exposure Questionnaire
TMG: Tokushukai Medical Group Database
WHO: World Health Organization

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Appendices

Appendix I. ICD-10 and K-codes for identification of Index Event.

Index Event	ICD-10 /K-codes
Non-fatal myocardial infarction (MI) diagnosis	▪ I21.0 Acute transmural MI of anterior wall ▪ I21.1 Acute transmural MI of inferior wall ▪ I21.2 Acute transmural MI of other sites ▪ I21.3 Acute transmural MI of unspecified site ▪ I21.4 Acute subendocardial MI ▪ I21.9 Acute MI, unspecified
Unstable angina diagnosis	▪ I20.0 Unstable angina
Urgent coronary revascularization procedure	▪ Z95.1 Presence of aortocoronary bypass graft ▪ Z95.5 Presence of coronary angioplasty implant and graft OR As defined in the Tokushukai Medical Database using the K-codes for identification of medical and surgical procedures. ▪ K5461 Percutaneous coronary intervention (for acute MI) ▪ K5462 Percutaneous coronary intervention (for unstable angina) ▪ K5463 Percutaneous coronary intervention (other) ▪ K547 Percutaneous coronary atherectomy ▪ K5481 Percutaneous coronary intervention (with special catheter) (with high-speed rotary percutaneous transluminal atherectomy catheter) ▪ K5482 Percutaneous coronary intervention (with special catheter) (with excimer laser coronary angioplasty catheter) ▪ K5483 Percutaneous coronary intervention (with special catheter) (with atherectomy-ablative angioplasty catheter) ▪ K5491 Percutaneous coronary artery stenting (for acute MI) ▪ K5492 Percutaneous coronary artery stenting (for unstable angina) ▪ K5493 Percutaneous coronary artery stenting (other) ▪ K550 Percutaneous transluminal coronary recanalization ▪ K550-2 Percutaneous coronary artery aspiration thrombectomy ▪ K5511 Coronary angioplasty (Thromboendarterectomy) (one site) ▪ K5512 Coronary angioplasty (Thromboendarterectomy) (2 or more sites) ▪ K5521 Coronary artery / Aortic bypass grafting (one anastomosis) ▪ K5522 Coronary artery / Aortic bypass grafting (2 or more anastomoses) ▪ K552-21 Coronary artery / Aortic bypass grafting (without the use of heart-lung machine) (one anastomosis) ▪ K552-22 Coronary artery / Aortic bypass grafting (without the use of heart-lung machine) (2 or more anastomoses)
Source of ICD-10 code definitions: https://icd.who.int/browse10/2019/en	

Appendix II. Additional data source descriptions.

Philip Morris Japan *IQOS* database	The Philip Morris Japan (PMJ) *IQOS* database includes information on registration of *IQOS* device (a type of heated tobacco product [HTP]). The data request form (DRF) completed by patients or their relatives will provide consent to access patients' HTP registration history from the PMJ database, by searching the database with a combination of personally identifiable information (PII) such as sex, email address, and phone number.
Points card business databases	Some points card businesses in Japan have fidelity programs that track purchases of tobacco products (eg, combustible cigarette [CIG] or HTP sticks). The DRF completed by patients or their relatives will provide consent to access patients' tobacco product purchase history from the points card business databases in Japan, by searching the database with a combination of PII.

Appendix III. ICD-10 codes for identification of study outcomes.

Outcomes	ICD-10 codes
Non-fatal myocardial infarction (MI) diagnosis	I21 Acute MI ▪ I21.0 Acute transmural MI of anterior wall ▪ I21.1 Acute transmural MI of inferior wall ▪ I21.2 Acute transmural MI of other sites ▪ I21.3 Acute transmural MI of unspecified site ▪ I21.4 Acute subendocardial MI ▪ I21.9 Acute MI, unspecified *I22 Subsequent MI* ■ I22.0 Subsequent MI of anterior wall ■ I22.1 Subsequent MI of inferior wall ■ I22.8 Subsequent MI of other sites ■ I22.9 Subsequent MI of unspecified site *I25.8 Other forms of chronic ischemic heart disease (Any condition in I21-I22 and I24 specified as chronic or with a stated duration of more than 4 weeks [more than 28 days] from onset)*
Non-fatal stroke diagnosis	I60 Subarachnoid hemorrhage ▪ I60.0 Subarachnoid hemorrhage from carotid siphon and bifurcation ▪ I60.1 Subarachnoid hemorrhage from middle cerebral artery ▪ I60.2 Subarachnoid hemorrhage from anterior communicating artery ▪ I60.3 Subarachnoid hemorrhage from posterior communicating artery ▪ I60.4 Subarachnoid hemorrhage from basilar artery ▪ I60.5 Subarachnoid hemorrhage from vertebral artery ▪ I60.6 Subarachnoid hemorrhage from other intracranial arteries I61 Intracerebral hemorrhage ▪ I61.0 Intracerebral hemorrhage in hemisphere, subcortical ▪ I61.1 Intracerebral hemorrhage in hemisphere, cortical ▪ I61.2 Intracerebral hemorrhage in hemisphere, unspecified ▪ I61.3 Intracerebral hemorrhage in brain stem ▪ I61.4 Intracerebral hemorrhage in cerebellum ▪ I61.5 Intracerebral hemorrhage, intraventricular ▪ I61.6 Intracerebral hemorrhage, multiple localized ▪ I61.8 Other intracerebral hemorrhage ▪ I61.9 Intracerebral hemorrhage, unspecified I62 Other nontraumatic intracranial hemorrhage ▪ I62.0 Nontraumatic subdural hemorrhage ▪ I62.1 Nontraumatic extradural hemorrhage ▪ I62.9 Intracranial hemorrhage (nontraumatic), unspecified I63 Cerebral infarction ▪ I63.0 Cerebral infarction due to thrombosis of precerebral

arteries
- I63.1 Cerebral infarction due to embolism of precerebral arteries
- I63.2 Cerebral infarction due to unspecified occlusion or stenosis of precerebral arteries
- I63.3 Cerebral infarction due to thrombosis of cerebral arteries
- I63.4 Cerebral infarction due to embolism of cerebral arteries
- I63.5 Cerebral infarction due to unspecified occlusion or stenosis of cerebral arteries
- I63.6 Cerebral infarction due to cerebral venous thrombosis, nonpyogenic
- I63.8 Other cerebral infarction
- I63.9 Cerebral infarction, unspecified

I64 Stroke, not specified as hemorrhage or infarction

I65 Occlusion and stenosis of precerebral arteries, not resulting in cerebral infarction
- I65.0 Occlusion and stenosis of vertebral artery
- I65.1 Occlusion and stenosis of basilar artery
- I65.2 Occlusion and stenosis of carotid artery
- I65.3 Occlusion and stenosis of multiple and bilateral precerebral arteries
- I65.8 Occlusion and stenosis of other precerebral artery
- I65.9 Occlusion and stenosis of unspecified precerebral artery

I66 Occlusion and stenosis of cerebral arteries, not resulting in cerebral infarction
- I66.0 Occlusion and stenosis of middle cerebral artery
- I66.1 Occlusion and stenosis of anterior cerebral artery
- I66.2 Occlusion and stenosis of posterior cerebral artery
- I66.3 Occlusion and stenosis of cerebellar arteries
- I66.4 Occlusion/ stenosis of multiple and bilateral cerebral arteries
- I66.8 Occlusion and stenosis of other cerebral artery
- I66.9 Occlusion and stenosis of unspecified cerebral artery

I67 Other cerebrovascular diseases
- I67.0 Dissection of cerebral arteries, nonruptured
- I67.1 Cerebral aneurysm, nonruptured
- I67.2 Cerebral atherosclerosis
- I67.3 Progressive vascular leukoencephalopathy
- I67.4 Hypertensive encephalopathy
- I67.6 Nonpyogenic thrombosis of intracranial venous system
- I67.7 Cerebral arteritis, not elsewhere classified
- I67.8 Other specified cerebrovascular diseases
- I67.9 Cerebrovascular disease, unspecified

G46 Vascular syndromes of brain in cerebrovascular diseases
- G46.0 Middle cerebral artery syndrome
- G46.1 Anterior cerebral artery syndrome
- G46.2 Posterior cerebral artery syndrome
- G46.3 Brain stem stroke syndrome

	▪ G46.4 Cerebellar stroke syndrome ▪ G46.5 Pure motor lacunar syndrome ▪ G46.6 Pure sensory lacunar syndrome ▪ G46.7 Other lacunar syndromes ▪ G46.8 Other vascular syndromes of brain in cerebrovascular diseases
Hospitalization for angina	▪ I20.0 Unstable angina ▪ I20.1 Angina pectoris with documented spasm ▪ I20.8 Other forms of angina pectoris ▪ I20.9 Angina pectoris, unspecified
Hospitalization for heart failure	▪ I50.0 Congestive heart failure ▪ I50.1 Left ventricular failure ▪ I50.9 Heart failure, unspecified
Urgent revascularization for angina	ICD-10 codes for angina (defined above) and procedure codes for urgent revascularization as defined in Appendix I.
All-cause mortality	Death due to any ICD-10 code
Hospitalization due to MI, unstable angina, or stroke	ICD-10 codes for MI, unstable angina, and stroke as defined above
Source of ICD-10 code definitions: https://icd.who.int/browse10/2019/en	

Appendix IV. Covariates to be extracted from the Tokushukai Medical Database.

- Date of birth
- Sex
- Income information
- Smoking status (smoking index [number of cigarettes per day and by years of smoking]), if available
- Height and weight
- Clinical laboratory information (eg, glycated hemoglobin)
- Comorbidities prior to the Index Event (**Appendix V**) with their date of occurrence:
    - Diabetes
    - Chronic obstructive pulmonary disease
    - Dyslipidemia
    - Cancer (any malignant type)
    - Hyperuricemia
    - Gout
    - Other cardiovascular disease (hypertension, peripheral vascular disease, stroke)

Appendix V. ICD-10 codes for identification of history of comorbidities prior to the Index Event.

Comorbidities	ICD-10 codes
Chronic obstructive pulmonary disease (COPD)	J41 Simple and mucopurulent chronic bronchitis ▪ J41.0 Simple chronic bronchitis ▪ J41.1 Mucopurulent chronic bronchitis ▪ J41.8 Mixed simple and mucopurulent chronic bronchitis J42 Unspecified chronic bronchitis J43 Emphysema ▪ J43.1 Panlobular emphysema ▪ J43.2 Centrilobular emphysema ▪ J43.8 Other emphysema ▪ J43.9 Emphysema, unspecified J44 Other chronic obstructive pulmonary disease ▪ J44.0 Chronic obstructive pulmonary disease with acute lower respiratory infection ▪ J44.1 Chronic obstructive pulmonary disease with acute exacerbation, unspecified ▪ J44.8 Other specified chronic obstructive pulmonary disease ▪ J44.9 Chronic obstructive pulmonary disease, unspecified
Diabetes	E11 Type 2 diabetes mellitus ▪ E11.0 Type 2 diabetes mellitus with coma ▪ E11.1 Type 2 diabetes mellitus with ketoacidosis ▪ E11.2 Type 2 diabetes mellitus with renal complications ▪ E11.3 Type 2 diabetes mellitus with ophthalmic complications ▪ E11.4 Type 2 diabetes mellitus with neurological complications ▪ E11.5 Type 2 diabetes mellitus with peripheral circulatory complications ▪ E11.6 Type 2 diabetes mellitus with other specified complications ▪ E11.7 Type 2 diabetes mellitus with multiple complications ▪ E11.8 Type 2 diabetes mellitus with unspecified complications ▪ E11.9 Type 2 diabetes mellitus without complications E14 Unspecified diabetes mellitus ▪ E14.0 Unspecified diabetes mellitus with coma ▪ E14.1 Unspecified diabetes mellitus with ketoacidosis ▪ E14.2 Unspecified diabetes mellitus with renal complications ▪ E14.3 Unspecified diabetes mellitus with ophthalmic complications ▪ E14.4 Unspecified diabetes mellitus with neurological complications ▪ E14.5 Unspecified diabetes mellitus with peripheral circulatory complications ▪ E14.6 Unspecified diabetes mellitus with other specified complications ▪ E14.7 Unspecified diabetes mellitus with multiple

	complications ▪ E14.8 Unspecified diabetes mellitus with unspecified complications ▪ E14.9 Unspecified diabetes mellitus without complications
Cancer	C00-C97 Malignant neoplasms
Stroke	As defined in Appendix II
Dyslipidemia	E78 Disorders of lipoprotein metabolism and other lipidemias ▪ E78.0 Pure hypercholesterolemia ▪ E78.1 Pure hyperglyceridemia ▪ E78.2 Mixed hyperlipidemia ▪ E78.3 Hyperchylomicronemia ▪ E78.4 Other hyperlipidemia ▪ E78.5 Hyperlipidemia, unspecified ▪ E78.6 Lipoprotein deficiency ▪ E78.8 Other disorders of lipoprotein metabolism ▪ E78.9 Disorder of lipoprotein metabolism, unspecified
Hyperuricemia	E79 Hyperuricemia ▪ E79.0 Hyperuricemia
Gout	M10 Gout ▪ M10.0 Idiopathic gout ▪ M10.1 Lead-induced gout ▪ M10.2 Drug-induced gout ▪ M10.3 Gout due to renal impairment ▪ M10.4 Other secondary gout ▪ M10.9 Gout, unspecified
Peripheral vascular disease	I70-I78 Diseases of arteries, arterioles, and capillaries
Source of ICD-10 code definitions: https://icd.who.int/browse10/2019/en	

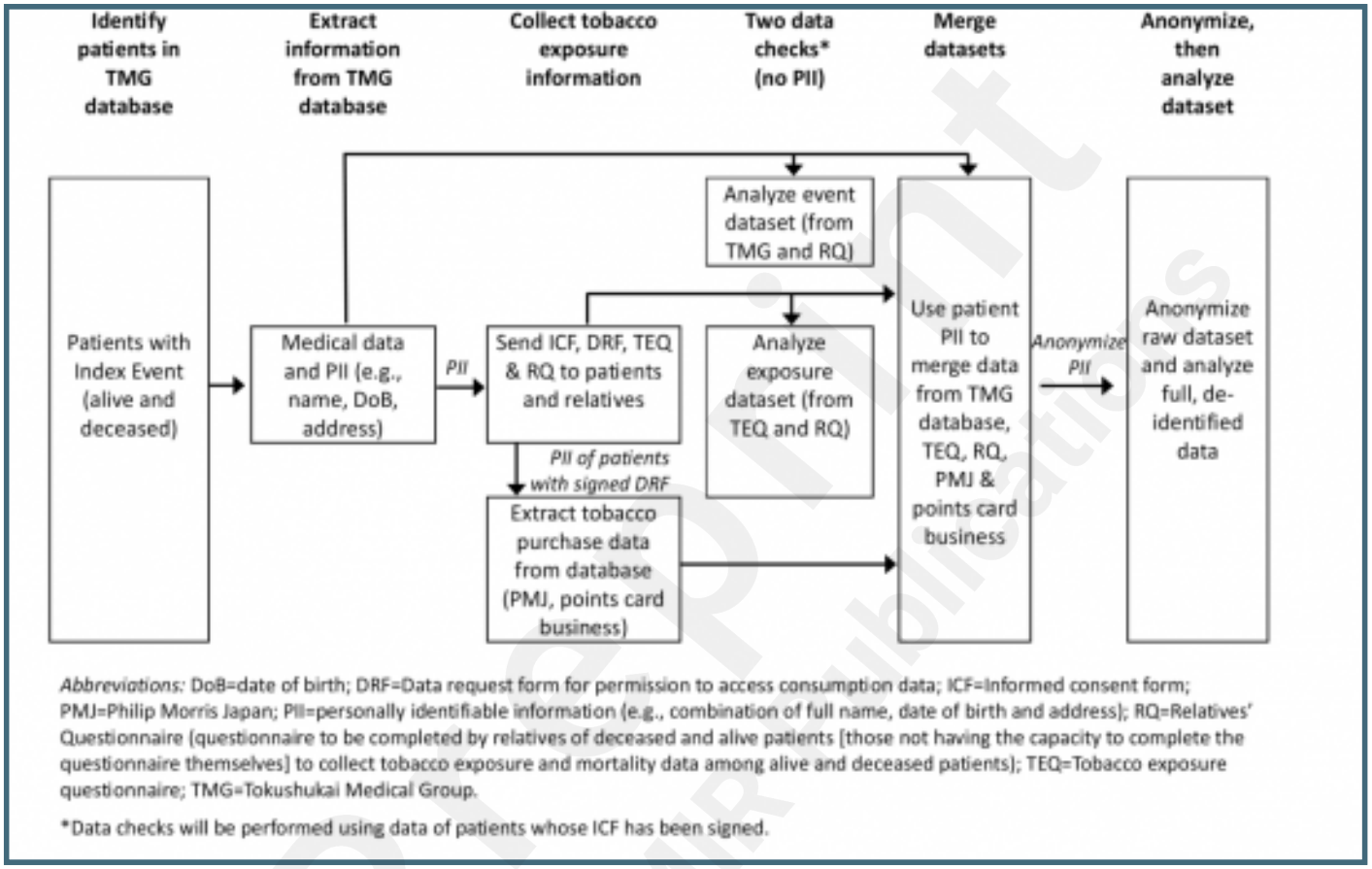
Appendix VI. Detailed sample size calculation assumptions.

Parameter	Assumed value	Rationale
Significance level, alpha	2.5%, one-sided	Based on the primary objective of the study
Power	90%	To reduce the risk of type II error
Index period	From May 1, 2016 to December 31, 2020	To allow enough time for a follow-up period
Average follow-up period	5 years	The average follow-up time in the meta-analysis [10] used for the yearly proportion of subsequent MACE was 5.4 years, and the Index Period of the planned study ends in 2020; the minimum follow-up period will be less than 4 years, and the maximum follow-up period will be 9 years
Ratio of CIG smokers to HTP users	2:1	Based on the number of current CIG smokers and HTP users in Japan in 2020 (prevalence of 25.9% vs 10.9% respectively)[28]
Proportion of CIG smokers having subsequent MACE over average study period (5.4 years)[8]	32.3%	From a systematic review and meta-analysis of subsequent MACE
Proportion of subsequent MACE in CIG smokers within a year[8]	7%	From a systematic review and meta-analysis of subsequent MACE
Estimated non-proportional HR after switching by year of follow-up (from internal simulated modeling data on years of life saved for stroke by introducing smoke-free products in the United States and Japan [32]) for the sole purpose of making sample size estimates.	Year 1: 0.95 Year 2: 0.86 Year 3: 0.79 Year 4: 0.73 Year 5: 0.68 Year 6: 0.65 Year 7: 0.62	Estimated non-proportional HR to account for the assumption of a delayed effect related to risk of a CVD event in HTP switchers due to the years of smoking compared to continued CIG smokers
Missing data after patient enrollment	10%	Assumption
Propensity score weighting inflation	30%	Assumption
Abbreviations: CIG, combustible cigarettes; CVD, cardiovascular disease; HTP, heated tobacco products; HR, hazard ratio; MACE, major adverse cardiovascular events.		

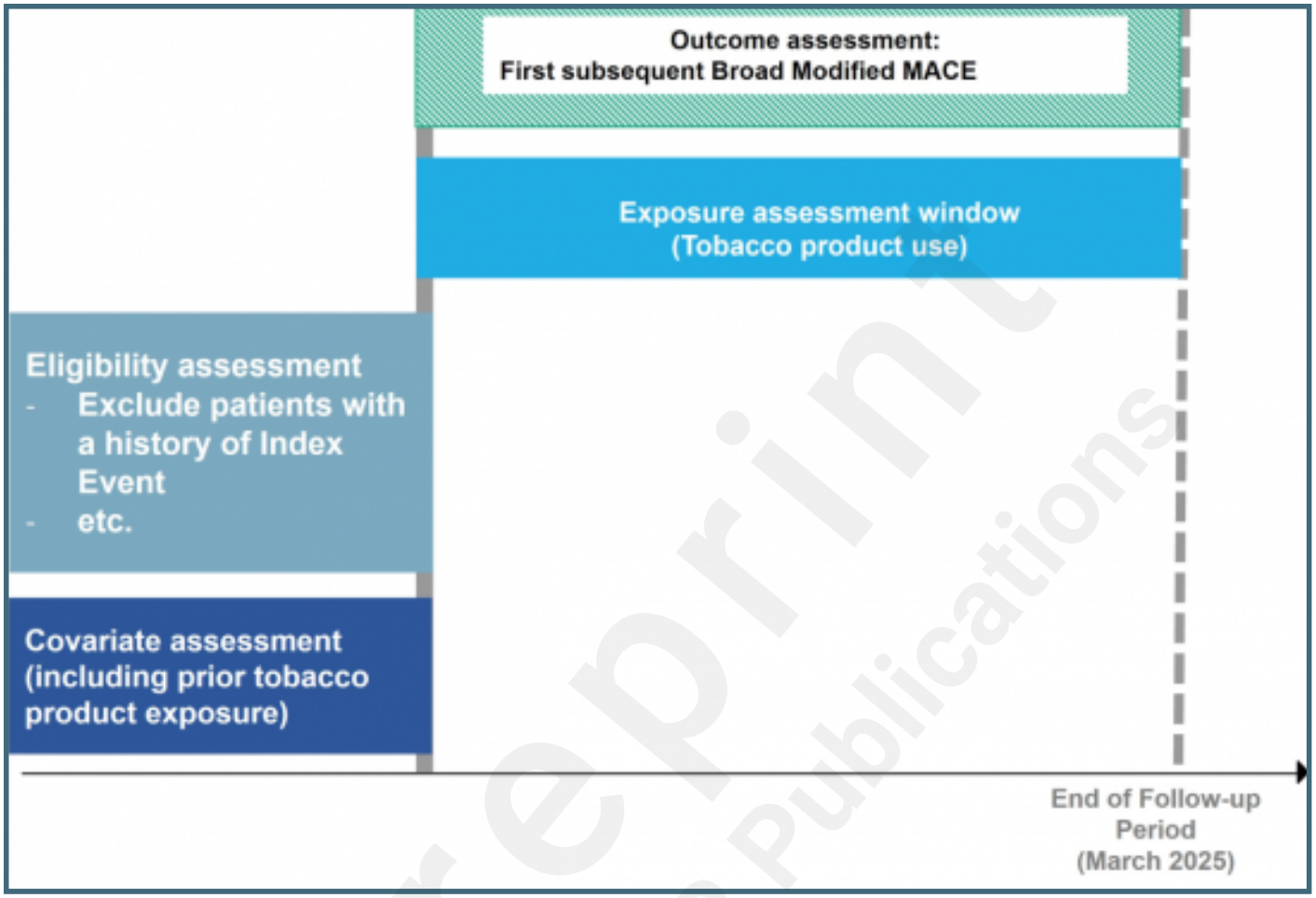
Supplementary Files

Figures

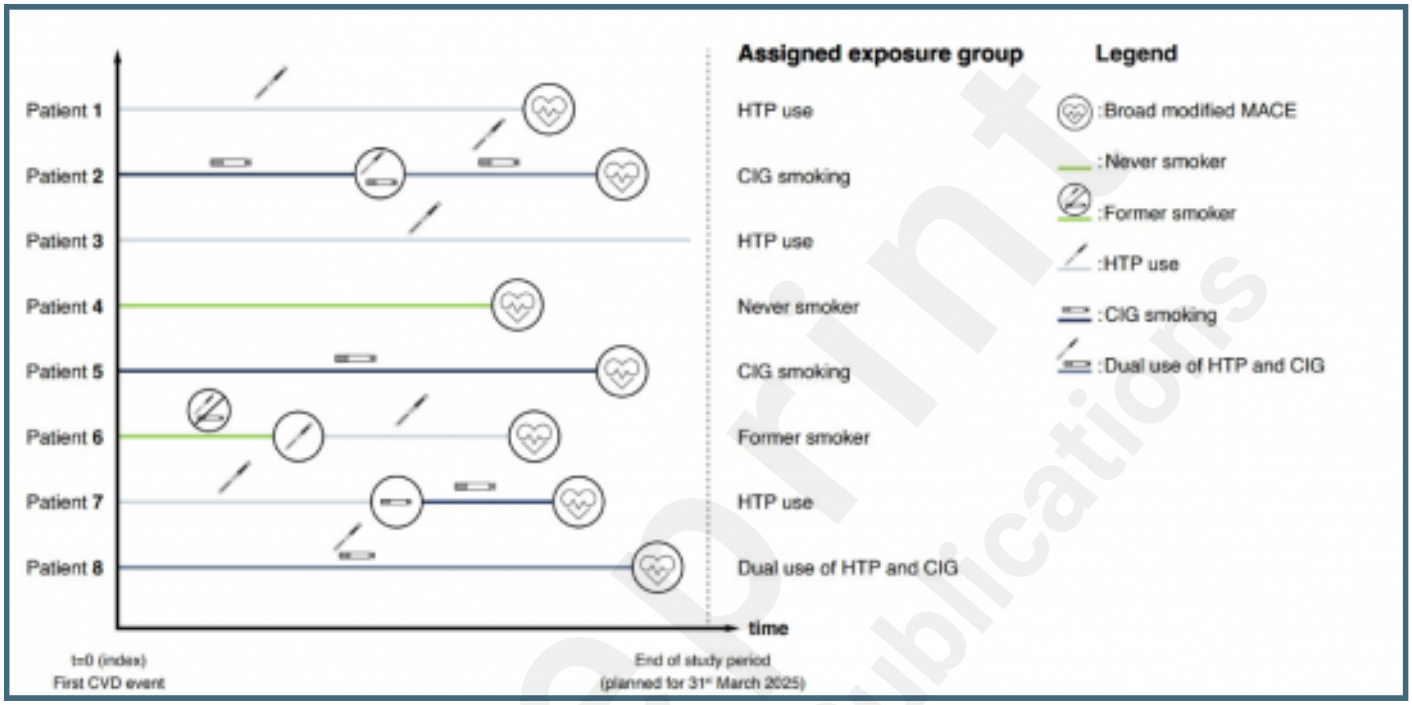
Overview of study design and data flow. DoB, date of birth; DRF, data request form for permission to access consumption data; ICF, informed consent form; PMJ, Philip Morris Japan; PII, personally identifiable information (eg, combination of full name, date of birth, and address); RQ, Relatives' Questionnaire (to be completed by relatives of deceased and alive patients [those unable to complete the questionnaire themselves] to collect tobacco exposure and mortality data); TEQ, Tobacco Exposure Questionnaire; TMG, Tokushukai Medical Group. *Data checks will be performed using data of patients whose ICF has been signed.



Study period overview. Note: The start of the exposure assessment window (here at Index Event) is illustrative and will be determined after data checks on exposure and events. MACE, major adverse cardiovascular event.



Classification of patients into exposure groups. Classification will happen before exploring associations with outcomes: (Figure 3) Exposure data expected to be collected, (Figure 4) Exposure data used to classify patients into exposure groups. The symbol 'X' in the figure represents patient censoring at the end of study period, and a circle with a product inside signifies a switch to use of that product. Note: The start of the exposure assessment window (here at index) is illustrative and will be determined after data checks on exposure and events. CIG, combustible cigarette; CVD, cardiovascular disease; HTP, heated tobacco product; MACE, major adverse cardiovascular event.



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