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TRIAL DESIGN

Rational and design of EACVI-MMVD study: an international registry on multimodality imaging for mixed and multiple valvular heart disease

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Abstract

Aims

Multiple and mixed valvular heart disease (MMVD) are frequent situations in clinical practice. Despite a high prevalence, comprehensive insights into their clinical presentation, management strategies, impact of multimodality imaging, and outcomes are not well established, due to a lack of dedicated studies.

Methods and results

The 'EACVI-MMVD Study' will be a large prospective, multicentre, observational cohort study led by the Heart Imagers of Tomorrow of the European Association of Cardiovascular Imaging (EACVI). It will assess the proportion, management, and prognosis of MMVD over a 1-year period of follow-up. All consecutive patients diagnosed with MMVD using transthoracic echocardiography will be recruited over a 6-month recruitment period in 88 centres from 24 different countries. Baseline evaluation will be determined by physicians and encompass the whole spectrum of multimodality imaging including transthoracic and transoesophageal echocardiography, stress echocardiography, computed tomography, and cardiovascular magnetic resonance. Centres will have the opportunity to send cardiovascular imaging data for core laboratory analysis and to extend recruitment throughout a 5-year follow-up period.

Conclusion

The EACVI-MMVD study will be the largest international multicentre study evaluating the prevalence of MMVD in clinical routine and determining the impact of multimodality cardiovascular imaging in MMVD patients.

Clinical Trial Registration: NCT06235385 URL: https://classic.clinicaltrials.gov/ct2/show/NCT06235385

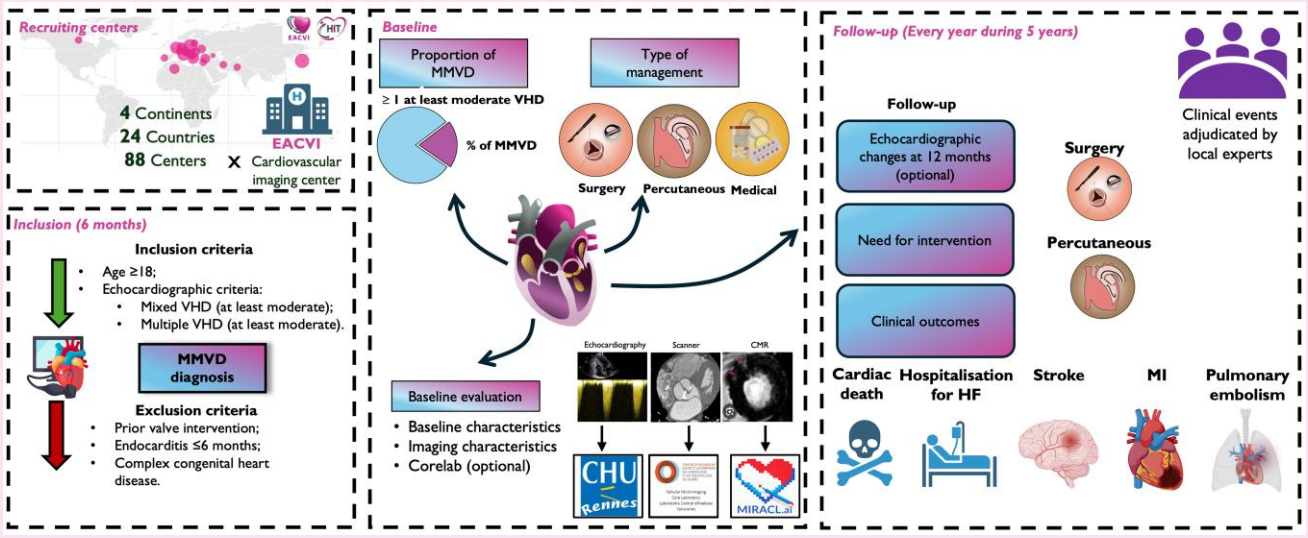
Lay summary

Multiple and mixed valvular heart disease (MMVD) refers to situations where more than one problem affects the heart valves. In multiple disease, several valves are abnormal in different ways. In mixed disease, the same valve has both narrowing and leakage. These conditions are frequent in everyday practice, yet they remain poorly understood. Unlike single valve disease, there are no large dedicated studies to guide doctors on how best to diagnose, treat, and follow patients with MMVD.

The EACVI-MMVD study has been created to address this gap. It is a large international project led by young cardiologists within the European Association of Cardiovascular Imaging. Over a 6-month period, 88 hospitals in 24 countries will recruit all patients diagnosed with MMVD. Doctors will record how the disease is first detected, which imaging tests are used, how treatment decisions are made, and how patients are doing one year later. The study will also assess the role of advanced imaging techniques, such as ultrasound scans, computed tomography, and magnetic resonance imaging, in guiding patient care.

By collecting data from thousands of patients worldwide, this will be the largest study ever conducted on MMVD. Its results are expected to improve knowledge, support better medical decisions, and ultimately help provide more effective and personalized care for people living with complex valve disease.

Graphical Abstract



Study design and workflow of the EACVI-MMVD registry.

Keywords multimodality imaging • valvular heart disease • multiple and mixed valvular heart disease • European Association of Cardiovascular Imaging (EACVI) • core laboratory • prognosis

Introduction

The burden of valvular heart disease (VHD) is increasing in high-income countries and represents a growing public health concern.[1] Among VHD cases, a large number of patients present with multiple and/or mixed VHD (MMVD). MMVD are defined as the combination of stenotic or regurgitant lesions occurring on ≥2 cardiac valves (i.e. multiple VHD) or the combination of stenotic and regurgitant lesions in the same valve (i.e. mixed VHD)[1–3] According to the international registry of valvular disease, up to 30% of patients with severe valvular disease present with multiple VHD.[4] Among patients with one disease valve, mixed VHD was found in 8.2%, mainly in the aortic position.[5] The US database of the Society of Thoracic Surgeons (1993–2007) revealed that 11% of patients requiring surgery for VHD had multiple VHD.[6] MMVD is a complex condition where the resulting consequences are influenced by several factors, including the unique combination of valve lesions, the timing and severity of their onset, the loading conditions imposed on the heart, and the effect on overall performance of the ventricles during both systole and diastole.[3] It is crucial to characterize this patient population more comprehensively since MMVD not only complicates the evaluation of VHD, but is also associated with poor outcomes.[3,7] An approach that includes multimodality cardiovascular imaging (MMI), such as echocardiography, cardiovascular magnetic resonance imaging (CMR) and cardiac computed tomography (CT), can offer a more detailed assessment of the severity and prognosis of MMVD within this intricate diagnostic framework.[3,8] Our understanding of how to manage patients with MMVD is limited, and whilst MMI appears to be a promising approach for evaluating these patients, there is a scarcity of data regarding its additional value[5,7–9] Due to the heterogeneity of this clinical scenario, various possible combinations, aetiologies and severities of VHD, previous studies have been typically conducted in single centres with a limited number of patients.[7,10] Due to a lack of evidence for the management of MMVD, current guidelines mainly focus on single VHD, leading to different approaches in different centres.[1] In the latest guidelines from the European Society of Cardiology (ESC), the section on combined and multiple valve disease occupies only half a page and does not include any specific recommendation for therapeutic management. Because of this major knowledge gap, the guidelines underline the urgent need for registries to evaluate MMVD and understand its natural history, aiming for a better understanding of the impact of management on prognosis.[1] Due to this significant lack of evidence in the literature, we advocate for initiating the 'European Association of Cardiovascular Imaging—Multiple and Mixed Valvular Heart Diseases' (EACVI-MMVD), the first international registry of MMVD. The objectives of the study across several international centres are as follows:

- To assess the proportion and epidemiological characteristics of MMVD within the VHD population;
- to evaluate the existing use of diagnostic methodologies across several countries, in particular different MMI approaches;
- to evaluate current management strategies;
- and to understand the prognosis of these MMVD patients.

This study will offer insights into the epidemiology, diagnosis, management, and prognosis of MMVD, bridging knowledge gaps and, eventually, to establish a basis for evidence-based management.

Design

Study population

The EACVI-MMVD study, endorsed by the EACVI and led by the Heart Imagers of Tomorrow (HIT), will be conducted as an international multicentre observational 'real-life' study spanning 88 centres affiliated with the EACVI network across 24 countries (official EACVI/ESC endorsement letter is available in Supplementary data online, *Figure S1*). The overview of the method is depicted in the *Graphical Abstract*. Centres will prospectively assess consecutive patients with at least one moderate or severe VHD referred to the cardiovascular imaging department

Table 1 Inclusion and exclusion criteria of the EACVI-MMVD study

Inclusion criteria	
	(1) Age ≥ 18 years
	(2) Patient referred to the cardiovascular imaging department.
	(3) Diagnosis of MMVD confirmed by transthoracic echocardiography, defined as:
	(a) Multiple VHD: at least two moderate to severe VHD involving ≥ 2 different valves, according to the current ESC guidelines.
	or
	(b) Mixed VHD: at least moderate stenosis and at least moderate regurgitation of a single valve, according to the current ESC guidelines
	(4) Patient not refusing to have their data involved in the protocol after information or accepting to have their data involved in the protocol after information.
Exclusion criteria (patients fulfilling any of the following criteria are not eligible for inclusion in this study)	(1) History of prior valve surgery or percutaneous valve intervention (note: it will be **no** exclusion criteria if it concerns a valve other than those involved in the definition of MMVD).
	(2) Acute infective endocarditis at the time of evaluation for inclusion (confirmed according to modified Duke criteria) or history of endocarditis ≤ 6 months.
	(3) Complex congenital heart diseases (such as single-ventricle physiology, transposition of the great arteries, Tetralogy of Fallot, and other complex malformations).

Of note, rheumatic valve disease, left ventricular assist device, heart transplantation, and systemic comorbidities were not systematically excluded.

over a 6-month period. Among those, all patients who meet the criteria for MMVD will be included in the study, followed by a 12-month period follow-up. Therefore, the baseline evaluation and management of each patient will be left to the attending physician's discretion in line with the current ESC guidelines.[1] The study has been approved by each local ethics committee complying with the principles outlined in the Declaration of Helsinki for research in human subjects. All patients will provide informed consent. Anonymized data supporting the findings of this study will be collected using Cleanweb™ software (Telemedicine Technologies, Boulogne-Billancourt, France) and will be available from the corresponding author upon reasonable request. The study has been registered on the ClinicalTrials.gov website (https://classic.clinicaltrials.gov/ct2/show/NCT06235385) under the identifier NCT06235385, and study data and results will be added upon completion of the study. All authors and investigators involved in this study have reviewed and approved the manuscript (the full list of EACVI-MMVD Study investigators is available in Supplementary data online, *Table S1*).

Definition of MMVD

The diagnosis of MMVD will be established by a senior cardiologist using transthoracic echocardiography, defined as (i) multiple VHD: at least two moderate-to-severe VHD involving ≥ 2 different valves and/or (ii) mixed VHD: at least moderate stenosis and at least moderate regurgitation of a single valve, according to the current ESC guidelines.[1] In addition, subgroup analyses will be conducted to evaluate mixed and multiple VHD separately, in order to provide specific insights into their epidemiology, management, and outcomes. All details regarding the inclusion and exclusion criteria are presented in *Table 1*. Patients with acute infective endocarditis were excluded. Prior valve interventions (surgical or percutaneous) were not considered exclusion criteria if they involved valves other than those defining MMVD. To promote consistency, Supplementary data online, *Table S2* presents quantitative criteria, in line with current guidelines and expert consensus, to define the severity of VHD diagnosis[11–13] The study will collect the number of excluded patients and those who decline participation to build the study flowchart.

Baseline characteristics and cardiovascular imaging

In the context of a 'real-life' cohort, the baseline evaluation, left to the attending physician's discretion, will encompass clinical characteristics, hospitalization reasons, cardiovascular medications, and past medical history, including chronic diseases and symptoms (see Supplementary data online, *Table S3*). Creatine and natriuretic peptide will be collected. A comprehensive transthoracic echocardiographic analysis will be conducted to determine the aetiology of VHD, evaluate left ventricular function and dimensions, pulmonary pressures, and VHD severity. The degree of mitral, aortic, pulmonary, and tricuspid stenosis/regurgitation will be evaluated using semi-quantitative and quantitative parameters, according to ESC and EACVI publications (all echocardiographic parameters collected are detailed in Supplementary data online, *Table S4*). All imaging parameters will be collected in absolute values, and subsequently indexed to body size (height, weight, body surface area) using a standardized formula across centres to ensure consistency. Further, within a three-month window before or after the initial echocardiography, additional assessments may include transoesophageal echocardiography, stress echocardiography (see Supplementary data online, *Table S5*), CMR[14] (see Supplementary data online, *Table S6*), cardiac CT exams (see Supplementary data online, *Table S7*), and diagnostic procedures like invasive coronary angiography and right heart catheterization. Additionally, the potential for concomitant cardiac amyloidosis will be assessed by collecting the performance and results of technetium-based bone scintigraphy and/or CMR and light chain detection if available.

Management of MMVD

At baseline, we will outline the decision-making process and therapeutic strategies for patients, including the choice between surgery, percutaneous interventions, or medical management. This will encompass determining which valves require treatment and will consider staged management. We will also address acute complications arising from interventional management and the potential need for rescue therapy. Comprehensive details regarding the interventions and complications collection are provided in Supplementary data online, *Table S8*.

Table 2 Primary and secondary endpoints of the EACVI-MMVD study

Primary endpoint	
Proportion of MMVD among all consecutive patients with a diagnosis of at least moderate VHD	
Secondary endpoints	
#1 Baseline characteristics	Epidemiologic distribution of clinical, biological, and cardiovascular imaging characteristics at baseline.
#2 Initial management	• Proportion of MMVD treated by surgery vs. percutaneous vs. medical • Proportion of MMVD according to the number of valves treated. • Proportion of the different staged management. • Proportion of acute complications of interventional management
#3 Prognostic	• Clinical composite outcome #1 at 1-year of follow-up defined as: cardiovascular mortality, hospitalization for heart failure* (HF), myocardial infarction, pulmonary embolism, and stroke. • Clinical composite outcome #2 (sensitivity analysis) at 1-year of follow-up defined as: cardiovascular mortality, hospitalization for heart failure, myocardial infarction, stroke, redo valve interventions, ventricular arrhythmias/ICD interventions, and infective endocarditis (excluding pulmonary embolism). • Individual outcome components are also reported separately at 1-year of follow-up. This follow-up will be repeated at 2, 3, 4, and 5 years.

Endpoints

The primary endpoint will be the proportion of MMVD including each combination of MMVD among all consecutive patients with a diagnosis of at least moderate VHD assessed in the cardiovascular imaging department.

All secondary endpoints are detailed in *Table 2* and will encompass the analysis of baseline characteristics demographics, biological, and MMI findings. Regarding the prognosis, all cardiovascular outcomes will be adjudicated, including cardiovascular mortality, hospitalization for heart failure, myocardial infarction, pulmonary embolism, and stroke. Regarding the prognosis, all cardiovascular outcomes will be adjudicated, including cardiovascular mortality, hospitalization for heart failure, myocardial infarction, pulmonary embolism, and stroke. These events constitute the composite outcome. In addition, a sensitivity analysis composite outcome was defined, including cardiovascular mortality, hospitalization for heart failure, myocardial infarction, stroke, redo valve interventions, ventricular arrhythmias, and infective endocarditis. Finally, all individual outcome components are reported separately. The complete list of major adverse cardiac events and definitions is provided in Supplementary data online, *Table S9*.

Follow-up

The 1-year follow-up will be conducted during a patient visit or through telephone/video-call contact with the patient's treating physician at each centre. All clinical events will be rigorously adjudicated locally by senior cardiologists. The information retrieved at this point is detailed in Supplementary data online, *Table S10* and encompasses vital status, assessment for dyspnoea, measurement of peptide natriuretic levels, the need for hospitalization due to cardiac reasons, and the need for a valvular intervention during the 12-month follow-up. Participating centres will be able to extend patient recruitment on an annual basis throughout a 5-year follow-up period, following the same rules of local adjudication. In addition, participating centres have the option to perform a second transthoracic echocardiographic examination at 12 months following the initial assessment.

Centre questionnaire

The centre questionnaire aims to characterize MMVD management across sites. Hospital characteristics, including type, location, and specialized units, will be recorded. information on medical staff, Heart Team organization, and imaging/interventional case volume will be included (see Supplementary data online, *Table S11*).

Multimodality cardiovascular imaging core laboratory

To increase the robustness of the study and gain an in-depth understanding in depth of the process behind MMVD, the EACVI-MMVD study involves several participating centres that send pseudo-anonymized cardiovascular imaging DICOM medical images through dedicated software to central core labs for analysis. This dataset, encompassing echocardiography, CT, and CMR images, is managed by the team of MIRACL.ai laboratory (*Multimodality Imaging for Research and Analysis Core Laboratory and Artificial Intelligence, AP-HP, Paris, France*), which oversees its storage and distribution to three international expert core laboratories:

- Echocardiographic images will be analysed by Prof. E. Donal and Prof. A Coisne at '*CHU Rennes Core Lab*' (Rennes Hospital, France).
- CT images will be evaluated by Prof. M.A. Clavel at '*VaRMI Core Lab*' (Quebec Heart and Lung Institute, Canada).
- CMR images will be processed by Dr. T. Pezel at '*MIRACL.ai laboratory*' (University Hospital of Lariboisiere, AP-HP, Paris, France).

Each core lab will engage independent experienced EACVI level III certified cardiovascular imagers to perform analysis. In cases of significant expert disagreement, a third specialist will be consulted. These labs will conduct comprehensive assessments of each imaging technique and various post-processing technologies, including strain analysis and artificial intelligence algorithms.

Statistical analysis

Sample size calculation

The sample size was calculated to accurately estimate the proportion of MMVD in patients with VHD, targeting a precision within a ± 2.5% margin of error at a 95% confidence interval. Leveraging data from the EURObservational Research Programme's survey,[4] we anticipate a minimum MMVD prevalence of 20% across the study population, necessitating the inclusion of 1500 patients to achieve the desired

statistical precision for our primary outcome. Recruitment will span six months across various centres, based on precedents from the EURObservational Research Programme.

Statistical methods

Continuous data will be reported as means ± standard deviation (SD) for normally distributed data or as medians and interquartile range for non-normally distributed data. Categorical data will be reported as counts and percentages. Between-groups comparisons will be performed using Student's *t*-test or Mann–Whitney test for continuous variables and using the chi-square or Fisher's exact test for categorical variables. Regarding the analysis of the clinical outcomes, logistic regression analysis will be used for the in-hospital outcomes. The cumulative incidence rates of outcomes after discharge will be estimated using Kaplan–Meier analysis and compared with the log-rank test. Patients lost to follow-up will be censored at the time of last contact. Multivariable Cox proportional hazards models will be used to identify independent predictors of outcomes. The study will allow to calculate several traditional risk scores like EuroScore-II, MAGGIC for heart failure, Charlson Comorbidity Index, MitraScore, and COAPT score, enabling sub-studies on their applications (see Supplementary data online, *Table S12*). In addition, prespecified subgroup analyses will be performed separately for mixed VHD and multiple VHD. Beyond traditional statistical analysis methods, we will explore the interest of clustering to provide new pathophysiological hypotheses in MMVD, and supervised machine learning methods to build new scores to predict outcomes in these patients. All data will be analysed using the R software, version 4.2.1 (R Project for Statistical Computing, R Foundation, Vienna, Austria) and Python software, version 3.12.4.

Discussion

Proportion and distribution of MMVD

Many experts have highlighted the lack of a prospective registry to investigate the MMVD population.[1,3,9,15] The EURObservational Research Programme Valvular Heart Disease II Survey, which focused on severe valve diseases in Europe and included patients who had undergone valvular interventions, did not specifically investigate all MMVDs, excluding cases of moderate MMVD (multiple and mixed).[4] Therefore, through consecutive recruitment, our study will be the first to evaluate mixed and multiple VHD together to fill this gap by determining the precise proportion of MMVD across participating centres, including moderate VHD.

Current diagnostic practice

The EACVI-MMVD study will evaluate the current diagnostic practices in each centre, including adherence to the ESC guidelines criteria used for diagnosis, employed imaging techniques, and diagnostic modalities used for MMVD patients. The coexistence of multiple VHDs represents one of the most challenging cardiovascular conditions for a cardiovascular imaging specialist. Several methods routinely used to assess VHD using echocardiography have not been validated in this subset of patients and may be misleading if not correctly interpreted in the context of the MMVD.[3,16,17] Growing evidence suggests that other imaging modalities, such as transoesophageal echocardiography, stress echocardiography, cardiac CT and CMR, can be helpful in VHD when conventional resting echocardiography is inconclusive.[3,8]

Centralized analysis by international core laboratories

One of the EACVI-MMVD study's great strengths is its ability to conduct cardiovascular image analyses by international centralized analysis core laboratories.[18] Recognizing that the evaluation of MMVD severity is one of the most challenging situations to evaluate in clinical routine for the cardiovascular imager this approach will improve the standardization and robustness of the imaging results. Additionally, we will analyse several parameters of MMVD's impact on the ventricles regarding remodelling and fibrosis.[19] Beyond assessing traditional cardiovascular imaging parameters, the core labs involved will investigate using new innovative post-processing tools using artificial intelligence.[20,21]

Management of MMVD patients

This study aims to analyse current management strategies for MMVD across centres, to identify trends, challenges, and opportunities to improve care. It will also provide insights into procedure-related complications and offer a comprehensive overview of worldwide practices, facilitating a discussion on potential improvements in MMVD management.

Prognosis of MMVD patients

An important aim of our study is to identify and validate biomarkers and imaging parameters for prognostic assessment in MMVD. We will evaluate BNP/NT-proBNP and multimodality imaging (echocardiography, CMR, CT) to improve risk stratification. Particular attention will be given to 12-month echocardiographic changes in moderate MMVD. Our recruitment strategy also enables evaluation of existing prognostic scores, and we will explore the potential of machine learning to develop novel risk models for this complex condition.[22]

Study limitations

First, although it will not include centres in the USA or South America to allow for worldwide generalizability, the inclusion of 24 countries on 4 continents, with a wide range of healthcare facilities, provides a comprehensive overview of the contemporary presentation and management of MMVD in the world. Second, the absence of valve intervention in some patients may be related to multiple causes such as patient refusals or procedural risks considered too high. The precise reasons for the lack of intervention cannot be collected in this study. Third, the main challenge in the evaluation of MMVD lies in the heterogeneity of combinations of VHD and variability in severity and mechanisms among valvular lesions. Ethnicity was not collected, as this variable can be ethically challenging in an international registry. Instead, by recruiting patients from 24 countries across 4 continents, the study captures geographical, socio-economic, and aetiological diversity. Fourth, this study reports proportions of MMVD characteristics and outcomes within the recruited cohort but does not aim to determine the prevalence of MMVD in the general population. Fifth, while there is no centralized adjudication of clinical events collected during follow-up, the implementation of local adjudication by a panel of senior cardiologists from each hospital is expected to enhance the overall quality of the follow-up data. Sixth, follow-up symptom assessment was restricted to the NYHA functional class; other patient-reported outcomes such as quality of life and additional symptoms (including oedema, palpitations, dizziness, syncope, and cardiogenic shock), as well as extensive biological parameters, were not systematically evaluated. Finally, advanced imaging parameters (such as right ventricular or atrial strain, regurgitant fraction, dimensionless index for aortic stenosis, stress testing variables, or detailed CMR and CT measurements) were not collected systematically across centres. However, the presence of multimodality core laboratories will allow dedicated ancillary analyses of these advanced parameters on subsets of the study population.'

Conclusions

The multicentric EACVI-MMVD study will serve as a valuable resource, providing a comprehensive understanding of the epidemiology,

aetiology, diagnosis methods, management approaches, and prognostic factors associated with different combinations of VHD worldwide. Through this collaborative effort, we can bridge the existing knowledge gaps and pave the way for evidence-based recommendations for the optimal management of MMVD.

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Supplementary data

Supplementary data are available at *European Heart Journal - Imaging Methods and Practice* online.

Author contributions

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Data availability

The data underlying this article are available from the principal investigator upon reasonable request and subject to approval by the study steering committee.

Lead author biography

Alexandre Unger is a cardiology specialist in training from Belgium and a doctoral candidate in cardiovascular imaging. His research focuses on advanced applications of cardiac magnetic resonance and multimodality imaging for risk stratification. Under the mentorship of Dr. Théo Pezel in Paris, the international coordinator of the EACVI-MMVD study, he contributed to the design and coordination of the EACVI-MMVD study.

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