# Study Report

# P3-C1-018

# DARWIN EU®- Prevalence of hypertrophic cardiomyopathy (HCM) and obstructive hypertrophic cardiomyopathy (oHCM) in six European countries

Authors: A. Saura-Lazaro, A. Prats-Uribe

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| **Author(s)** | Anna Saura-Lazaro (a.sauralazaro@darwin-eu.org)<br>Albert Prats-Uribe (a.prats-uribe@darwin-eu.org) |

# TITLE

DARWIN EU® - Prevalence of hypertrophic cardiomyopathy (HCM) and obstructive hypertrophic cardiomyopathy (oHCM) in six European countries

# 1. DESCRIPTION OF STUDY TEAM

| Study team role(s) | Name(s) | Organisation(s) |
|---|---|---|
| Principal Investigator | Albert Prats-Uribe<br>Anna Saura-Lazaro | University of Oxford |
| Data Scientist | Edward Burn<br>Marta Alcalde-Herraiz | University of Oxford |
| Epidemiologist | Albert Prats-Uribe<br>Anna Saura-Lazaro | University of Oxford |
| Clinical Domain Expert | Albert Prats-Uribe<br>Anna Saura-Lazaro | University of Oxford |
| Study Manager | Natasha Yefimenko | Erasmus MC |
| **Data partner name*** | **Data Partner member name(s)** | **Organisation(s)** |
| CPRD-GOLD | Antonella Delmestri<br>Hezekiah Omulo | University of Oxford |
| DK-DHR | Claus Møldrup<br>Elvira Bräuner<br>Susanne Bruun<br>Monika Roberta Korcinska Handest | Danish Medicines Agency |
| InGef RDB | Josephine Jacob<br>Raeleesha Norris<br>Annika Vivirito<br>Alexander Harms | Institut für angewandte Gesundheitsforschung Berlin GmbH |
| NAJS | Jakov Vuković, Ivan Pristaš, Anamaria Jurčević<br>Marko Čavlina, Antea Jezidžić De Pero Ivanko | Croatian Institute of Public Health |
| NLHR | Hedvig Nordeng<br>Nhung Trinh<br>Saeed Hayati<br>Maren Mackenzie Olson | University of Oslo |
| SIDIAP | Talita Duarte Salles<br>Anna Palomar<br>Augustina Giuliodori Picco | IDIAPJGol |

*Data partners' role is only to execute code at their data source, review and approve their results. These people do not have an investigator role. Data analysts/programmers do not have an investigator role and thus declaration of interests (DOI) for these people is not needed.

# 2. DATA SOURCES

**Table 1.** Description of the selected data sources.

| Country | Name of Database | Justification for Inclusion | Health Care setting | Type of Data | Number of active subjects | Feasibility count of HCM | Data lock for the last update |
|---|---|---|---|---|---|---|---|
| UK | CPRD-GOLD | The database has information on HCM diagnosis and treatments done in primary care or feedbacked to the GP from the specialists. The denominator is suitable for population rates as it includes all people registered in the GP practice. | Primary care | EHR | 2.92 million | 7,800 | 17/10/2024 |
| DK | DK-DHR | The database has information on HCM diagnosis performed in hospitals and specialist offices and treatments administered in hospital. The denominator is suitable for population rates as it includes the entire population. | Community pharmacists, secondary care – specialists, hospital inpatient care | Registries | 5.96 million | 13,700 | 15/05/2014 |
| DE | InGef RDB | The database has information on HCM diagnosis and treatments done in primary care or hospital. The denominator is suitable for population rates as it includes the entire population insured. | Primary care, community pharmacists, primary care specialists, secondary care-specialists, hospital inpatient care* | Claims | 7.6 million | 12,400 | 17/06/2024 |
| CR | NAJS | The database has information on HCM diagnosis and treatments performed in primary care or hospital. The denominator is suitable for population rates as it includes population insured. | Primary care, secondary care-specialists, hospital inpatient care | Claims | 2.68 million | 10,700 | 07/08/2024 |
| NO | NLHR | The database has information on HCM diagnosis performed in hospitals and specialist offices and treatments administered in hospital Denominator is suitable for population rates as it includes all population. | Primary care, primary care specialists, secondary care-specialists, hospital inpatient care | Registries | 6.11million | 12,500 | 18/01/2024 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| ES | SIDIAP | data on HCM diagnosis performed in primary care or inpatient and primary care treatments. Denominator is suitable for population rates as it includes all people registered in the GP practice. | Primary care with hospital linkage | EHR | 5.95 million | 23,400 | 20/03/2023 |

CR = Croatia, DE = Germany, DK = Denmark, ES = Spain, NO = Norway, UK = United Kingdom, CPRD = Clinical Practice Research Datalink, DK-DHR = Danish Data Health Registries, InGef RDB= InGef Research Database CPRD, NAJS = Croatian National Public Health Information System, NLHR = Norwegian Linked Health Registry data, SIDIAP = Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària

*This study considered only inpatient diagnoses to avoid potential misclassification of the index date, as quarterly outpatient diagnoses are recorded with a single date.

Number of active subjects is defined as the maximum number of persons in an observation period, in the last 6 months.

# 3. ABSTRACT

**Title**

DARWIN EU® – Prevalence of hypertrophic cardiomyopathy (HCM) and obstructive hypertrophic cardiomyopathy (oHCM) in six European countries

**Rationale and background**

Hypertrophic cardiomyopathy (HCM) is the most common genetic heart disease, defined by an increased wall thickness or mass of the left ventricular wall and characterised by a broad clinical spectrum. Some individuals remain undiagnosed due to the absence of significant symptoms or the need for major interventions. When left ventricular outflow tract (LVOT) obstruction is present, the condition is classified as obstructive HCM (oHCM), which occurs in approximately 66% of patients.

The prevalence of HCM was initially estimated at 1 in 500 individuals (0.2%) in a U.S. study. However, subsequent studies with varied designs and cohort characteristics have reported lower prevalence estimates for clinically recognised HCM cases. While these variations warrant further investigation, large-scale epidemiological studies on the demographics, morbidity burden, and clinical characterisation of HCM in Europe remain scarce.

**Research question and objectives**

The general objective of this study was to characterise hypertrophic cardiomyopathy (HCM) and obstructive HCM (oHCM) in six European countries in terms of prevalence, demographics, HCM-related comorbidities, diagnostic measurements, medications, and treatment procedures.

The specific objectives of this study were:

1. To estimate the annual prevalence of clinically recognised HCM and oHCM in six European countries, overall and stratified by age and sex.
2. To characterise patients with HCM and oHCM in terms of demographics, selected HCM-related comorbidities and diagnostic measurements existing before, at the time of, and after the first recorded HCM or oHCM diagnosis.
3. To describe the frequency of selected HCM-related medications and treatment procedures, before, at the time of, and after the first recorded HCM or oHCM diagnosis.

**Methods**

We conducted a retrospective cohort study including real-world data from six data sources across six European countries: two large primary care data sources (Clinical Practice Research Datalink (CPRD) GOLD, United Kingdom (UK) and Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària (SIDIAP), Spain), two Nordic nationwide registries that include both primary and secondary/hospital data (Danish Data Health Registries (DK-DHR), Denmark and Norwegian Linked Health Registry data (NLHR), Norway), and two nationwide claims databases (InGef Research Database (InGef RDB), Germany and Croatian National Public Health Information System (NAJS), Croatia) with InGef RDB only including hospital data. The study population consisted of all individuals aged 18 years or older with a first recorded diagnosis of HCM or oHCM between January 1st, 2010 (or the earliest available data) and end of available data in each database.

For objective 1, we estimated annual period prevalence from January 1st to December 31st, defined as the number of HCM and oHCM diagnoses divided by the total active population, stratified by age and sex. For objectives 2 and 3, we described the absolute and relative frequency of predefined HCM-related comorbidities, diagnostic measurements (e.g., echocardiography, imaging, LVOT, genetic testing), medications, and treatment procedures (e.g., cardiac pacemaker, defibrillator, septal reduction therapy,

heart transplantation) based on clinical expertise and previous literature. These were assessed before, at, and after the first recorded HCM or oHCM diagnosis (index date) across different time windows. Lastly, we estimated the median and interquartile range (IRQ) for the time from first record of each predefined variable to the index date.

**Results**

Over 40,200 individuals with HCM were identified across databases, out of which 20.92% (SIDIAP) to 59.76% (CPRD-GOLD) had a specified oHCM diagnosis. The proportion of men in the HCM cohort ranged from 52.35% (NAJS) to 62.75% (CPRD-GOLD), with a median age of 57 (IQR: 47-66) to 68 years (IQR: 56-78) for men and 67 (IQR: 56-76) to 78 years (IQR: 68-84) for women. In the oHCM cohort, men comprised 43.04% (SIDIAP) to 60.73% (CPRD-GOLD and InGef RDB), with a median age of 57 (IQR: 46-65) to 68 years (IQR: 59-77) for men and 67 (IQR: 57-78) to 76 years (IQR: 66-83) for women.

HCM prevalence increased over time across all databases, reaching values ranging from 0.043% (95%CI: 0.041–0.046) in CPRD-GOLD in 2023 to 0.237% (95%CI: 0.233–0.241) in SIDIAP in 2022. The prevalence trend for oHCM mirrored that of HCM but values remained consistently lower, ranging from 0.027% (95%CI: 0.025–0.029) in CPRD-GOLD to 0.069% (95%CI: 0.067–0.072) in NLHR in 2023. HCM prevalence was generally higher in men, although sex differences were less pronounced in the oldest age group (80+ years), where women had similar or higher prevalence than men (CPRD-GOLD, DK-DHR, InGef RDB, NAJS, NLHR). For oHCM, prevalence remained higher in men, but sex differences were overall less pronounced compared to HCM. HCM prevalence also increased with age, peaking in the oldest age groups—a pattern also observed for oHCM.

Essential hypertension, cardiac arrhythmia, ischemic heart disease, and heart failure were the most commonly recorded comorbidities among individuals with HCM and oHCM before and after the first recorded HCM or oHCM diagnosis. Valvular heart disease was more common among individuals with oHCM. Measurement data were generally underreported across most databases. When available (mainly in InGef RDB and NAJS), echocardiography, cardiac catheterization, Holter echocardiogram and magnetic resonance imaging, and left ventriculogram were the most frequently recorded measurements for both HCM and oHCM in the three months prior to the first recorded diagnosis.

Beta-blockers, diuretics, and ACE inhibitors were the most commonly recorded medications before and after the first recorded HCM or oHCM diagnosis. InGef uniquely captured the use of mavacamten, although its recorded frequency was very low (<1%). Procedure data were generally sparse across databases. When available (mostly in InGef RDB and NAJS), pacemaker and defibrillator implantation, and septal reduction therapy were the most frequently recorded procedures, with the latter being more common among individuals with oHCM. Lastly, most comorbidities, measurements, medications, and procedures had high frequencies before the first recorded diagnosis of HCM or oHCM, with the first record occurring more than a year before.

**Discussion**

This is the largest epidemiological study to date to provide valuable insights into the prevalence, demographics, clinical characteristics, and treatment, among individuals with HCM and oHCM across multiple European countries. The increasing prevalence over time aligns with trends observed in earlier studies and likely reflects advances in diagnostic capabilities and improved clinical awareness. Prevalence estimates varied across databases, likely due to differences in data sources, diagnostic methods, healthcare settings, and population characteristics. Age and sex distributions were also consistent with previous studies, showing that HCM and oHCM increased with age and was higher among men, except in the oldest age group (80 years and older). This, together with the fact that women were older at the first recorded

diagnosis, suggests that women may experience a delayed diagnosis, a pattern previously described in the literature.

Cardiac comorbidities and HCM-related medications were also aligned with previous studies. Notably, the high frequency of cardiac comorbidities and HCM-related treatments first recorded more than one year before the first recorded HCM or oHCM diagnosis suggests that there might be a long latency from symptoms to diagnosis. Additionally, the coexistence of hypertension with HCM remains a subject of debate, as hypertension is known to also cause left ventricular hypertrophy, and some studies have excluded hypertensive patients. Our study's findings, with essential hypertension being one of the most common comorbidities, underscore the need for a better understanding of this coexistence.

These findings enhance our understanding of the burden of this genetic heart disease on healthcare systems across Europe. They underscore the growing need for increased diagnostic awareness among clinicians and may inform the development and evaluation of future screening and management strategies, including the recent introduction of mavacamten.

# 4. LIST OF ABBREVIATIONS

| Acronyms/terms | Description |
|---|---|
| ACE | Angiotensin Converting Enzyme |
| AF | Atrial Fibrillation |
| ASMD | Absolute standard mean difference |
| CARDIA | Coronary Artery Risk Development in Young Adults |
| CDM | Common Data Model |
| CI | Confidence Interval |
| CPRD | Clinical Practice Research Datalink |
| CT | Compute Tomography |
| DARWIN EU® | Data Analysis and Real World Interrogation Network |
| DK-DHR | Danish Data Health Registries |
| EHR | Electronic Health Records |
| HCM | Hypertrophic cardiomyopathy |
| HF | Heart Failure |
| InGef RDB | InGef Research Database |
| IQR | Interquartile Range |
| LV | Left Ventricle |
| LVEF | Left Ventricular Ejection Fraction |
| LVOT | Left Ventricular Outflow Tract |
| MRI | Magnetic Resonance Imaging |
| NAJS | National Public Health Information System |
| NLHR | Norwegian Linked Health Registry data |
| oHCM | Obstructive hypertrophic cardiomyopathy |
| OHDSI | Observational Health Data Sciences and Informatics |
| UK | United Kingdom |
| U.S. | United States |
| SCD | Sudden Cardiac Death |
| SIDIAP | Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària |
| SNOMED | Systematized Nomenclature of Medicine |

# 5. AMENDMENTS AND UPDATES

None.

# 6. MILESTONES

| Study deliverable | Timelines (planned) | Timelines (actual) |
|---|---|---|
| Final Study Protocol | December 2024 | December 2024 |
| Creation of Analytical code | December 2024 | December 2024 |
| Execution of Analytical Code on the data | January 2025 | January 2025 |
| Draft Study Report | February 2025 | February 2025 |
| Final Study Report | March 2025 | April 2025 |
| Draft Manuscript (if agreed on) | May 2025 | |
| Final Manuscript (if agreed on) | July 2025 | |

# 7. RATIONALE AND BACKGROUND

**Definition and aetiology**

Hypertrophic cardiomyopathy (HCM) is an inherited heart disease characterised by an increased wall thickness or mass of the left ventricular wall, with a broad clinical spectrum. The diagnosis of HCM requires the presence of hypertrophy of the left ventricle (LV) in the absence of any other cardiac, metabolic, or systemic disease (e.g., systemic hypertension) that could explain the observed hypertrophy.(1)

In up to 60% of adolescents and adults with HCM, the disease follows an autosomal dominant inheritance pattern due to mutations in genes encoding cardiac sarcomere proteins.(2) Approximately 20% of HCM patients have a family history of sudden cardiac death, and 50% have evidence of familial disease. (2) It is also important to recognise that other conditions can mimic genetic forms of HCM, including mitochondrial diseases, Danon disease, Friedreich's ataxia, Leopard syndrome, Noonan syndrome, Anderson–Fabry disease, and amyloidosis.(3)

HCM is classified into two types based on the presence or absence of left ventricular outflow tract (LVOT) obstruction, a distinction that influences patient management. The obstructive form of HCM (oHCM) is observed in approximately 66% of patients, while the non-obstructive form accounts for around 33%.(4,5) oHCM is associated with a higher likelihood of developing symptoms compared to non-obstructive HCM. (6,7)

**Epidemiology**

HCM is the most common inherited genetic cardiomyopathy and a significant cause of cardiovascular morbidity and mortality across all age groups. Despite this, the absolute number of individuals diagnosed with HCM remains low, suggesting that the condition is likely underdiagnosed.(8) The prevalence of HCM in the general population was initially estimated to be approximately 1 in 500 individuals (0.2%), based on the CARDIA (Coronary Artery Risk Development in Young Adults) cohort study, which used standard

echocardiography in 4,111 unrelated individuals 23 to 35 years of age from four urban areas in the United States (U.S.).(9) The participants were randomly selected from community-based urban centres, where many affected individuals were asymptomatic and undiagnosed. This aligns with the observation that the majority of HCM patients are asymptomatic and remain undiagnosed during their lifetime. Subsequent studies, with varied designs and cohort characteristics, have supported this prevalence estimate across different age groups and ethnicities.(10–14)

However, the population-level prevalence estimate contrasts sharply with an analysis of U.S. claims data, which reported a much lower prevalence of clinically diagnosed HCM, at approximately 1 in 3,000 (0.03%).(15) Similarly, a study conducted in Germany examining trends in HCM prevalence from 2011 to 2015 found a rate of 0.07% in 2015, (3) and studies conducted in the United Kingdom (UK) and Sweden reported rates of 3.5 per 10,000 and 0.04% respectively, among the general population.(16,17) These discrepancies might be partially explained by the challenges in diagnosing this condition. It has been suggested that some individuals may live normal lifespans undiagnosed because the absence of significant symptoms or major interventions. As a result, the prevalence of clinically recognised HCM is much lower.

In terms of sociodemographic characteristics, the German study showed that HCM prevalence increased gradually with age from 7.4/100,000 persons (95% confidence interval (95%CI) 5.2–10.1) in those aged 0–9 years, to 298.7/100,000 persons (95% CI 276.4–322.4) in individuals over 80 years.(3) In all age groups, men had higher prevalence than women, with significant differences in patients over 30 years of age. A similar trend was observed in a nationwide retrospective cohort study in Denmark, which included 3,856 patients diagnosed with HCM between 2005 and 2018.(18) The median age at diagnosis was 68 years (interquartile range 56–78) with the majority of patients being male (53%). However, females were older (72 years vs. 63 years) and more likely to have oHCM (54% vs. 38%). Additionally, a study conducted in the UK, which aimed to estimate the population-diagnosed prevalence of cardiomyopathies between 2010 and 2018, found that HCM was twice as common among men.(17) Lastly, in children, HCM accounts for approximately 40% of paediatric cases of cardiomyopathy, making it the second most common cardiomyopathy after dilated cardiomyopathy.(19)

**Comorbidities and disease progression**

Patients with HCM have an increased risk of cardiovascular complications, including atrial fibrillation (AF), stroke, heart failure (HF), and sudden cardiac death (SCD).(1,20,21) Reported rates of AF varied widely, ranging from 4% in newly diagnosed patients to 33% in hospitalised patients. Managing AF in HCM patients can be challenging, as symptoms and haemodynamic changes are often poorly tolerated. Additionally, HCM patients with AF have a higher risk of thromboembolic events compared to AF patients without HCM.(1,20,22) Reported stroke rates range from 4% in a multinational registry study of patients who received care at an HCM specialty centre to 9.2% in hospitalised patients with HCM and AF.(2) The rate of HF-related events ranges from 15% in a multinational registry in pregnant women to 43% in a natural history study in patients at a specialty centre.(2) A systematic literature review of studies published between 1996 through 2016, examining the prevalence of HF among children and adolescents, identified one study reporting a 13.5% prevalence rate for congestive HF in paediatric patients with HCM.(23)

In the nationwide retrospective cohort study conducted in Denmark, which assessed temporal trends in patient characteristics, there was a significant decline in the prevalence of HF (from 20% in 2005 to 12% in 2018, $p<0.001$) and ischaemic heart disease (from 31% in 2005 to 16% in 2019, $p\leq0.001$)(18). However, the prevalence of AF and stroke remained high and unchanged throughout the study period. Notably, the rate of hospitalisations decreased over time (from 64% in 2005 to 46% in 2016, $p<0.001$), while the rate of outpatient follow-up increased (from 81% in 2005 to 87% in 2016, $p=0.003$).(18)

**Clinical management and treatment**

The primary aim of pharmacological therapy in HCM is to control symptoms, improve exercise capacity, reduce, or eliminate dynamic intraventricular gradients, treat LV dysfunction and HF, manage AF and ventricular arrhythmias, and prevent cardioembolic events.(24)

Until 2022, there were no targeted or disease-modifying treatments specifically approved for HCM. Pharmacotherapies for symptomatic relief typically include β-blockers as first-line treatment, titrated to the maximally tolerated dose, followed by non-dihydropyridine calcium-channel blockers (e.g., diltiazem or verapamil) or disopyramide. Surgical interventions are available for patients with the most severe form of oHCM and include alcohol septal ablation and septal myectomy, which can be effective in reducing obstruction and improving outflow of the LV, but do not address the underlying myocardial disease. Additionally, medical device implants such as implantable cardioverter defibrillators and pacemakers may be used to prevent oHCM-related SCD. However, these are invasive procedures requiring specialised clinical settings and may not be accessible to all patients.

In 2022, mavacamten, the first targeted treatment for symptomatic oHCM, was approved in the U.S. Mavacamten is a cardiac myosin inhibitor that works by normalising cardiac contractility, reducing dynamic LVOT obstruction, and improving cardiac filling pressures. The U.S. Food and Drug Administration (FDA) granted initial approval for its use in adults with symptomatic oHCM.(25) In 2023, the European Medicines Agency (EMA) also approved mavacamten for use in Europe.(26)

**Justification of the study**

Estimating the prevalence of HCM has proven problematic due to several factors, including the relative rarity of the condition, the high proportion of asymptomatic patients, and diagnostic challenges as it can be easily mistaken for other conditions presenting with hypertrophy of the LV.(18) Furthermore, fragmentation across healthcare databases can hinder accurate estimation, as patient follow-up may be incomplete. For example, diagnosis might occur in primary healthcare or after a hospitalization due to a complication. As a result, large-scale epidemiological studies on the demographics and morbidity burden of HCM in Europe are scarce, with many existing studies relying solely on inpatient records that do not capture the full extent of the disease burden. Additionally, the Cardiomyopathy Registry of the EURObservational Research Programme is a prospective registry study that reports on baseline data and contemporary management of adult patients with cardiomyopathies, however the design did not allow to estimate population prevalence of specific phenotypes.(27) This is because it was not set as a nationwide registry and therefore it has information only on cases but lack of a population denominator.

This study aimed to address these gaps by estimating the prevalence of HCM and oHCM on a large scale across several European countries. It also aimed to provide valuable insights into the characteristics of patients with HCM, including demographics, comorbidities, and treatment regimens. By incorporating a broader range of data sources, this approach contributed to a more accurate understanding of the population-level prevalence of HCM in Europe, which is essential for improving diagnosis and management across diverse populations.

# 8. RESEARCH QUESTION AND OBJECTIVES

The general objective of this study was to characterise hypertrophic cardiomyopathy (HCM) and obstructive HCM (oHCM) in six European countries in terms of prevalence, demographics, HCM-related comorbidities, diagnostic measurements, medications, and treatment procedures.

The specific objectives of this study were:

1. To estimate the annual prevalence of clinically recognised HCM and oHCM in six European countries, overall and stratified by age and sex.

2. To characterise patients with HCM and oHCM in terms of demographics, selected HCM-related comorbidities and diagnostic measurements existing before, at the time of, and after the first recorded HCM or oHCM diagnosis.
3. To describe the frequency of selected HCM-related medications and treatment procedures before, at the time of, and after the first recorded HCM or oHCM diagnosis.

All results were reported overall and stratified by age and sex for each data source.

# 9. RESEARCH METHODS

## 9.1 Study type and study design

The study consisted of a retrospective cohort design including patients with a first diagnosis of HCM or oHCM. We performed **a population-level descriptive epidemiology,** and a **patient-level characterisation** study classified as "off-the-shelf" and as described in the DARWIN EU® Complete Catalogue of Standard Data Analyses (Standardised Analytics).

**Table 2.** Description of potential study types and related study designs.

| Study type | Study design | Study classification |
|---|---|---|
| Population-level descriptive epidemiology | Population-level cohort | Off the shelf |
| Patient-level characterisation | Cohort analysis. | Off the shelf |

## 9.2 Study setting and data sources

This study was conducted using routinely collected health data from six databases in six European countries. All databases were previously mapped to the OMOP CDM.

Data sources:

1. Clinical Practice Research Datalink (CPRD) GOLD, United Kingdom (UK)
2. Danish Data Health Registries (DK-DHR), Denmark
3. InGef Research Database (InGef RDB), Germany
4. Croatian National Public Health Information System (NAJS), Croatia
   Norwegian Linked Health Registry data (NLHR), Norway
5. Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària (SIDIAP), Spain

We selected six out of the 28 databases onboarded in DARWIN EU® in 2024. The selection of databases for this study was performed based on data reliability and relevance for the proposed research question. The selected databases fulfil the criteria required for a population and patient-level characterisation study, while covering different settings and regions of Europe. Detailed information on the selected data sources and their ability to answer the study research questions are described in **Table 1.**

## 9.3 Study period

The study period covered from 01/01/2010, or from when accurate data become available in each database (i.e., 2015 for InGef, and 2014 for NAJS), until the end of available data in each of the data sources (see **Table 3**).

**Table 3.** Study period by database.

| Database | Start date | End date |
|---|---|---|
| CPRD-GOLD | 01/01/2010 | 15/06/2024 |
| DK-DHR | 01/01/2010 | 15/03/2024 |
| InGef RDB | 01/01/2015 | 30/09/2024 |
| NAJS | 01/01/2014 | 30/01/2025 |
| NLHR | 01/01/2010 | 31/12/2023 |
| SIDIAP | 01/01/2010 | 30/06/2023 |

## 9.4 Follow-up

For all objectives, follow-up started on the date of first recorded HCM or oHCM diagnosis (index date) and continued until the earliest of the following: 1) loss to follow-up, 2) date of death, or 3) end of observation period (the most recent data available) in the database.

## 9.5 Study population with inclusion and exclusion criteria

The study population included all individuals with a first recorded diagnosis of HCM or oHCM (index date) identified in the database during the study period and with at least one year of medical history. The index dates are defined in **Figure 1**.

The following eligibility criteria were applied for all study objectives (see **Figure 1**):

**General population cohort**

**Inclusion criteria:**

- Age ≥18 years.

- Present in the database within the study period.

- At least 365 days of prior medical history available before contributing follow-up time in the study.

**Newly diagnosed HCM or oHCM cohort**

**Inclusion criteria:**

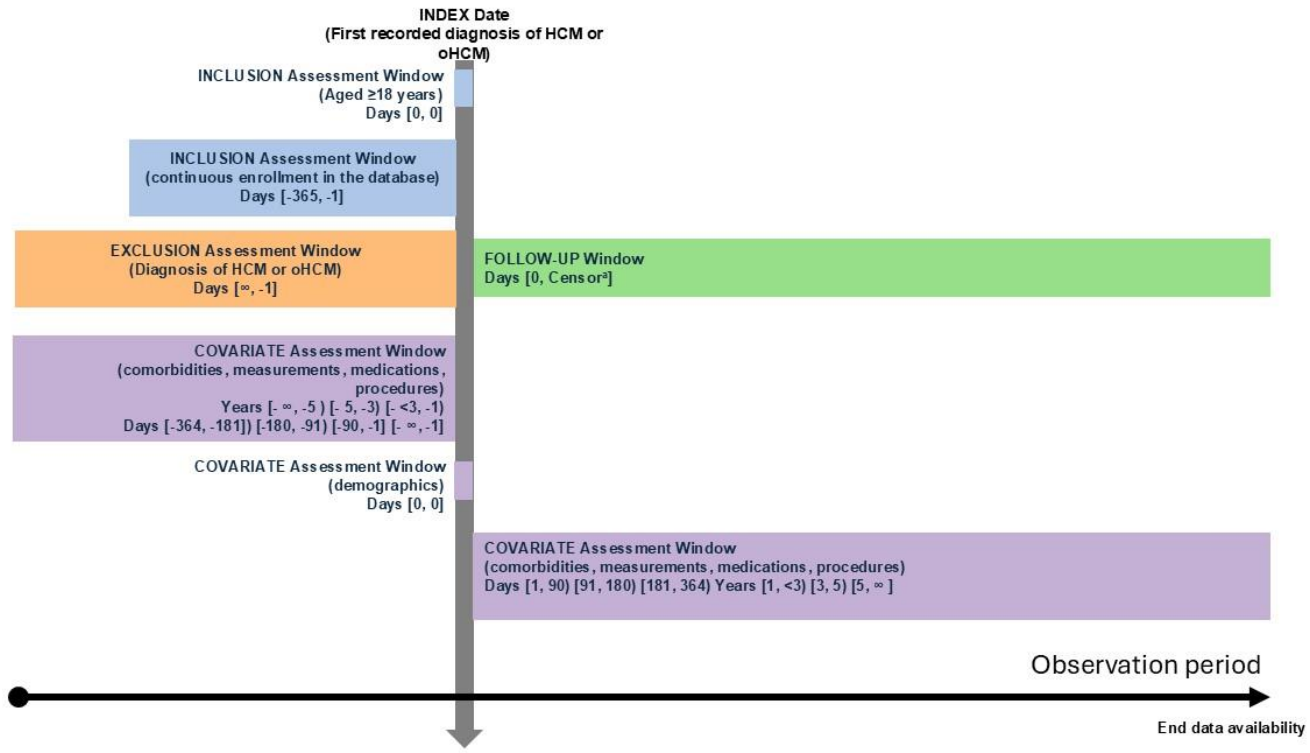
- Age ≥18 years.

- First recorded diagnosis of HCM or oHCM in the database during patient selection period.

- At least 365 days of prior history available before date of first recorded HCM or oHCM diagnosis.

**Exclusion criteria:**

-Any diagnosis of HCM or oHCM prior to index date.




a: follow-up until the earliest of loss to follow-up, end of data availability, or death

**Figure 1.** Study design diagram.

## 9.6 Variables

### 9.6.1 Main condition of interest

For objective 1, the condition of interest was defined as the first recorded diagnosis of HCM and oHCM, which was identified through the diagnosis codes defined by SNOMED. Only clinically recognised diagnosis that led to a healthcare encounter and generated a diagnosis were therefore captured. Additionally, conditions that can mimic genetic forms of HCM, including mitochondrial diseases, Danon disease, Friedreich's ataxia, Leopard syndrome, Noonan syndrome, Anderson–Fabry disease, and amyloidosis, were excluded.

### 9.6.2 Other covariates, including confounders, effect modifiers and other variables

**Covariates**

For objective 2, age and sex (female/male) at first recorded HCM or oHCM diagnosis were described. The following age grouping were used: 18-29, 30-39, 40-49, 50-59, 60-69, 70-79, 80 and over. Additionally, predefined comorbidities and measurements were identified using SNOMED and LOINC codes. These included:

Comorbidities: aberrant premature complexes, AF, atrioventricular block , cardiac arrhythmia (AF, ventricular fibrillation, (sustained) ventricular arrythmia, premature atrial, nodal or ventricular complexes, sick sinus syndrome, atrioventricular block), chronic kidney disease, chronic obstructive pulmonary disease, coronary arteriosclerosis, disorders of lipoprotein and/or lipid metabolism, essential hypertension, HF, ischaemic stroke, ischaemic heart disease, obesity, premature atrial contraction, SCD, sustained ventricular tachycardia, type 2 diabetes mellitus, valvular heart disease, and ventricular fibrillation.

Measurements: cardiac catheterisation, cardiac magnetic resonance imaging (MRI), computed tomography (CT) of the heart , echocardiography, endomyocardial biopsy, exercise test, genetic test, LVOT, Holter electrocardiogram, LVEF, and maximum LV thickness. Of note, DK-DHR and NLHR had no mapped data on the predefined measurements. For objective 3, predefined HCM medications and procedures were identified using RxNorm and SNOMED codes. These included:

- Medications: angiotensin converting enzyme (ACE) inhibitors, aldosterone antagonists, amiodarone systemic, angiotensin II receptor blockers, beta blocking agents, digoxin systemic, direct factor Xa inhibitors, diuretics, enoxaparin, heparin group, mavacamten, platelet aggregation inhibitors excluding heparin, selective calcium channel blockers with direct cardiac effects, and vitamin K antagonists. These were reported at class level, with the exception of cases when a single agent from the class was used (amiodarone, digoxin, enoxaparin, mavacamten).
- Procedures: cardiac pacemaker, cardioverter defibrillator, septal reduction therapy (alcohol septal ablation, surgical septal myectomy), transplantation of heart, and transplantation of heart valve.

Comorbidities, measurements, medications, and procedures were assessed in different time windows before and after first recorded HCM or oHCM diagnosis (see section 9.8.1 Main statistical methods). For medications, number of persons initiating or continuing the medication in the respective time windows were reported.

## 9.7 Study size

No sample size was calculated as this was a descriptive study which did not test a specific hypothesis. In addition, to estimate the prevalence of HCM or oHCM, we used already collected available data. Thus, the sample size was driven by the availability of patients with conditions of interest within each database.

## 9.8 Statistical methods

### 9.8.1 Main statistical methods

**Table 4**. Description of study types and type of analysis.

| Study type | Study classification | Type of analysis |
|---|---|---|
| Population-level descriptive epidemiology | Off-the-shelf | Period prevalence of disease |
| Patient-level characterisation | Off-the-shelf | Characterisation of selected variables |

**Federated Network Analyses**

Analyses were conducted separately for each database. Before study initiation, test runs of the analytics were performed on a subset of the data sources and quality control checks were performed (see Section 11 Quality control). Once all the tests were passed, the final package was released in the version-controlled Study Repository for execution against all the participating data sources.

The data partners locally executed the analytics against the OMOP Common Data Model (CDM) in R Studio and reviewed and approved the - by default - aggregated results before returning them to the Coordination Centre.

The study results of all data sources were checked after which they were made available to the team in the Digital Research Environment so the Study Dissemination Phase could start. All results were locked and timestamped for reproducibility and transparency.

**Patient privacy protection**

Cell suppression was applied as required by databases to protect people's privacy. Cell counts <5 were masked.

**Statistical model specification and assumptions of the analytical approach considered**

Population-level descriptive epidemiology

For objective 1, we estimated the period prevalence on an annual basis, defined as the period from January 1st to December 31st for each year. It was calculated as the number of individuals diagnosed with HCM and oHCM divided by the total active population, with complete persistence (i.e., a patient once diagnosed, is considered to have the diagnosis from the first occurrence until the end of follow-up). Participants were required to contribute a minimum of only one day within the period (and to have a diagnosis) to be included for the numerator. For inclusion in the denominator, participants were required to contribute a minimum of 6 months within the period.

All estimates were provided overall and stratified by age—allowing individuals to contribute to multiple age groups after the index date—and sex, along with 95%CI calculated using the Wilson method.(28)

Patient-level characterisation

Patient-level characterisation was conducted for objectives 2 and 3, both overall and by grouping patients diagnosed before 2020 and those diagnosed in 2020 or later in order to see potential trends in patients' characteristics.

For objective 2, age and sex at the time of first recorded HCM or oHCM diagnosis were described. The absolute number and percentage of patients with records of predefined comorbidities and receiving predefined measurements(as defined in Section 9.6 Variables) were assessed across the following non-overlapping time intervals, capturing each record of each comorbidity and measurement: >5 years, 5 to 3 years, <3 to 1 year, 364 to 181 days, 180 to 91 days, 90 to1 days before the index date, and during the periods 1 to 90 days, 91 to 180 days, 181 to 364 days, 1 to <3 years, 3 to 5 years, >5 years after the index date, with the denominator being the patients still observed at each time point (**Figure 1**). The time windows were selected based on the clinical likelihood of patients to exhibit symptoms before the formal diagnosis. A patient could be counted in more than one comorbidity and measurement.

For objective 3, the number and percentage of patients with records of each predefined medication and procedure (as defined in Section 9.6 Variables) were assessed across the following non-overlapping time intervals, capturing each record of each medication and procedure: >5 years, 5 to 3 years, <3 to 1 year, 364 to 181 days, 180 to 91 days, 90 to1 days before the index date, and during the periods 1 to 90 days, 91 to 180 days, 181 to 364 days, 1 to <3 years, 3 to 5 years, >5 years after the index date, with the denominator being the patients still observed at each time point (**Figure 1)**. A patient could be counted in more than one treatment group. Exposure started at date of the first prescription of each drug. For each prescription, the estimated duration of use was retrieved from the drug exposure table in the CDM. Subsequent prescriptions were combined into continuous exposed episodes (drug eras) if the distance in days between the end of first prescription and start of the second was 30 days or less. Additionally, the number and percentage of patients with a record of each comorbidity, measurement, and treatment (medications and procedures) prior to the index date were assessed for the entire available observation period, without

considering specific time intervals, in order to describe the presence of the covariates at any time before the first recorded HCM or oHCM diagnosis (**Figure 1**). Furthermore, we reported the median and interquartile range (IQR) of the time from the predefined covariates to first recorded HCM or oHCM diagnosis (if they first occurred before). As an exploratory analysis, we included a comparison of these predefined covariates with a random sample from the general population matched by age and sex. The identification of predefined comorbidities, measurements, medications, and procedures was concept-based (including descendants).

For all continuous variables, mean with standard deviation and median with IQR were reported. For all categorical analyses, number and percentages were reported. A minimum cell count of 5 was used when reporting results, with any smaller counts reported as "<5". All analyses were reported by country/database, overall and stratified by age and sex when possible (i.e., if the minimum cell count was reached).

**Software**

All analyses were performed with R. We used the following R packages:

- "IncidencePrevalence" (v1.0.0) (https://github.com/darwin-eu/IncidencePrevalence) for the computation of prevalence.(29)

- "CohortCharacteristics" (v0.4.0) (CRAN: Package CohortCharacteristics) for the patient-level characterization of demographics, clinical measurements, comorbidities, and treatment.
- "visOmopResults" (v1.0.0) (https://darwin-eu.github.io/visOmopResults/) for computing tables and figures.

### 9.8.2 Missing values

All variables used in the study were based on the recorded comorbidities, measurements, medications, and procedures, codes available in the data. We assumed that missing records for a respective variable indicated that the corresponding comorbidity, measurement, medication, or procedure was not present for the patient.

### 9.8.3 Sensitivity analysis

As a sensitivity analysis, we estimated the point prevalence of HCM and oHCM on an annual basis as of January 1st each year.

# 10. DATA MANAGEMENT

**Data management**

All databases were mapped to the OMOP CDM. This enabled the use of standardised analytics and tools across the network since the structure of the data and the terminology system had been harmonised. The OMOP CDM is developed and maintained by the Observational Health Data Sciences and Informatics (OHDSI) initiative and is described in detail on the wiki page of the CDM: https://ohdsi.github.io/CommonDataModel and in The Book of OHDSI: http://book.ohdsi.org

The analytic code for this study was written in R. Each data partner executed the study code against their database containing patient-level data and then returned the results set which only contained aggregated data. The results from each of the contributing data sites were combined in tables and figures for the study report.

**Data storage and protection**

For this study, participants from various European Union member states processed personal data from individuals, which was collected in national/regional electronic health record (EHR) databases. Due to the sensitive nature of this personal medical data, it was important to be fully aware of ethical and regulatory aspects and to strive to take all reasonable measures to ensure compliance with ethical and regulatory issues on privacy.

All databases used in this study had already been used for pharmaco-epidemiological research and had a well-developed mechanism to ensure that European and local regulations dealing with ethical use of the data and adequate privacy control were adhered to. In agreement with these regulations, rather than combining person level data and performing only a central analysis, local analyses were run, which generated non-identifiable aggregate summary results.

# 11. QUALITY CONTROL

**General database quality control**

A number of open-source quality control mechanisms for the OMOP CDM have been developed (see Chapter 15 of The Book of OHDSI http://book.ohdsi.org/DataQuality.html). In particular, it was expected that data partners had run the OHDSI Data Quality Dashboard tool (https://github.com/OHDSI/DataQualityDashboard). This tool provides numerous checks relating to the conformance, completeness, and plausibility of the mapped data. Conformance focuses on checks that describe the compliance of the representation of data against internal or external formatting, relational, or computational definitions, completeness in the sense of data quality was solely focused on quantifying missingness, or the absence of data, while plausibility seeks to determine the believability or truthfulness of data values. Each of these categories had one or more subcategories and was evaluated in two contexts: validation and verification. Validation relates to how well data align with external benchmarks with expectations derived from known true standards, while verification relates to how well data conform to local knowledge, metadata descriptions, and system assumptions.

**Study specific quality control**

When defining HCM and oHCM, a systematic search of possible codes for inclusion was identified using CodelistGenerator R package (https://github.com/darwin-eu/CodelistGenerator). This software allowed the user to define a search strategy and using this, queried the vocabulary tables of the OMOP Common Data Model so as to find potentially relevant codes. The codes returned were reviewed by two clinical epidemiologists to consider their relevance. In addition, we ran phenotype diagnostics to assess the use of different codes across the databases contributing to the study and identify any codes potentially omitted in error (30):

- The diagnostics used to review the conditions of interest (HCM and oHCM) included counts of the population of interest, attrition, code counts of the condition of interest in the overall database, counts of potential missing codes related to the condition of interest, counts of codes of interest at cohort index date, distribution of age, sex and time observed before and after index; cohort overlap and timing between different conditions of interest (including different flavours for the same condition), incidence and prevalence in a sample of the database, and a large scale characterisation of the individuals with the condition of interest (sampled if necessary) including a comparison with a random sample from the general population matched by age and sex (the large scale characterisation allowed us to see how different was the cohort we identified from population of same age and sex). The large-scale characterisation also allowed us to confirm the available data, particularly the counts on clinical measurements and procedures.

This allowed for a consideration of the validity of the study cohort of patients in each of the databases and confirmed that multiple definitions were not required.

The study code was based on two R packages developed to (1) estimate prevalence, (2) characterise demographic, clinical characteristics, and treatments. These packages included numerous automated unit tests to ensure the validity of the codes, alongside software peer review and user testing. The R package was made publicly available via GitHub.

# 12. RESULTS

All results are available in an interactive web application ("shiny app") at P3-C1-018. The shiny app consists of four main tabs:

1. Background – Provides a brief description of the study, including the rationale, background, and objectives.
2. Study databases – Includes a Snapshot subtab with a table summarising metadata for each study database.
3. Study cohorts – Contains five subtabs:
    - Cohort code use – Displays codes from the study code list used to phenotype HCM or oHCM observed on the day of cohort entry.
    - Cohort attrition – Presents cohort attrition by study eligibility criteria in both table and plot formats.
    - Cohort characteristics – Displays selected patient-level variables at different time windows before, at, and after the index date, available in both table and plot formats.
    - Large-scale characteristics – Displays the top 50 patient-level concepts available, including conditions, drugs, measurements, observations, procedures, and healthcare visits per database, cohort, stratification, and time window.
    - Compare large-scale characteristics – Displays a comparison of the study cohorts and a random sample from the general population matched by sex and age. It includes the frequency of concepts in, both groups as well as the standardised mean differences, allowing identification of concepts that are more frequently observed in the HCM cohorts compared to the sex- and age-matched sample.
4. Population estimates – Includes one subtab:
    - Prevalence – Displays population-level prevalence rates in both table (raw data) and plot formats.

The shiny app includes two cohorts:

- HCM (HCM_narrow) – All individuals with HCM, regardless of the form.
- oHCM (HCM_obstructive) – Individuals with the obstructive form of HCM.

## 12.1 Participants

**Figure 2** presents a flowchart illustrating the attrition at each stage of the eligibility criteria applied to the HCM and oHCM cohorts across study databases.

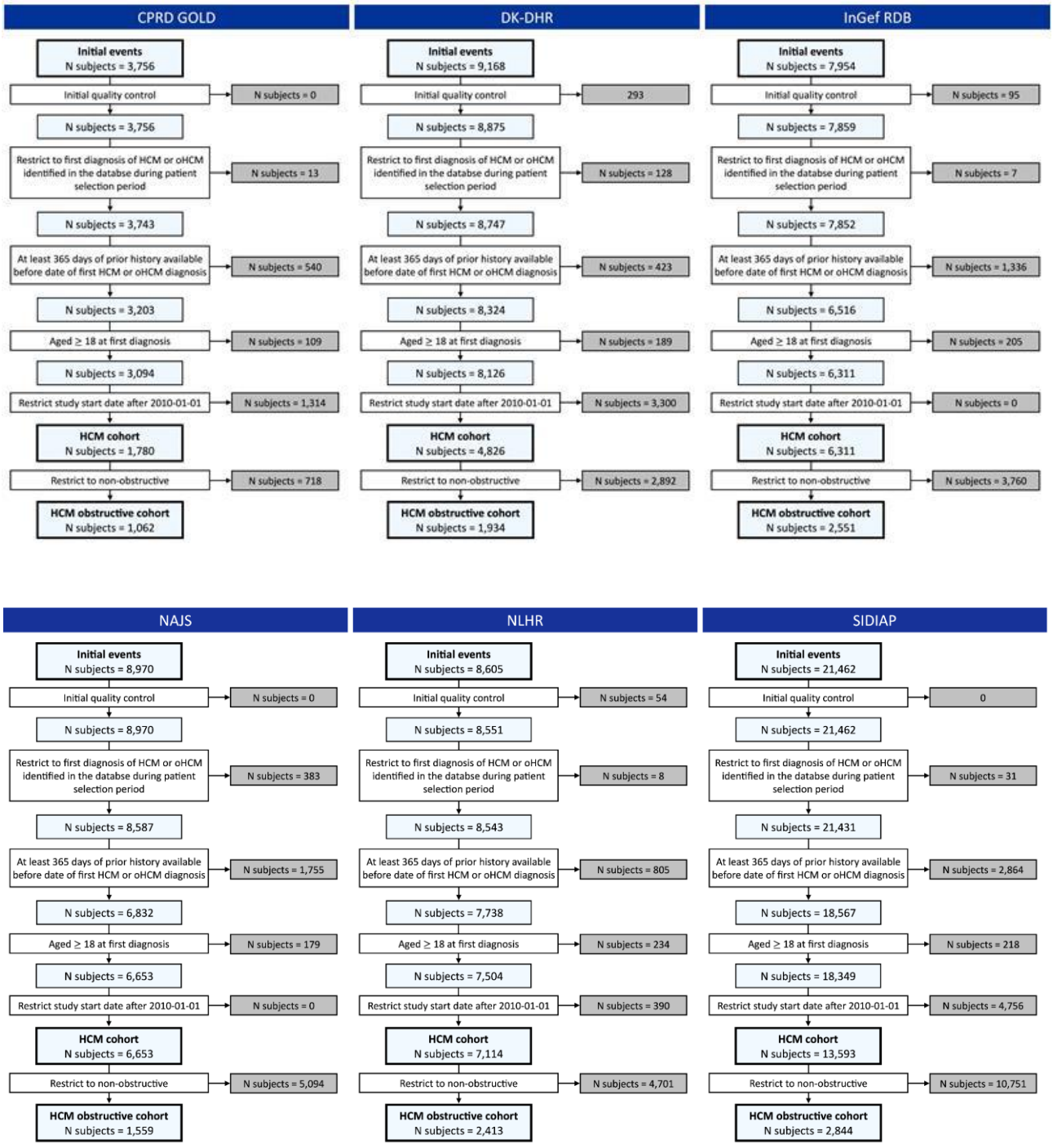



**Figure 2.** Attrition flowchart of HCM and oHCM cohorts by study database
Initial quality control includes restricting to those with a start date prior to the end date, ensuring they were recorded while the individual was under observation, merging overlapping records, and retaining only the first diagnosis.

We identified over 40,200 individuals with HCM across all study databases: 1,780 individuals in CPRD-GOLD; 4,826 in DK-DHR; 6,311 in InGef RDB; 6,653 in NAJS; 7,114 in NLHR; and 13,593 in SIDIAP. Among them, 1,062 (59.76%) in CPRD-GOLD; 1,934 (40.07%) in DK-DHR; 2,551 (40.42%) in InGef RDB; 1,559 (23.43%) in NAJS; 2,413 (33.92%) in NLHR; and 2,844 (20.92%) in SIDIAP were part of the oHCM cohort.

Among individuals in the HCM cohort across different databases, the percentage of men ranged from 52.35% (NAJS) to 62.75% (CPRD-GOLD) (Table 5), with a median age ranging from 57 years (IQR: 47-66) (CPRD-GOLD) to 68 years (IQR: 56-78) (SIDIAP) for men and from 67 years (IQR: 56-76) (CPRD-GOLD) to 78 years (IQR: 68-84) (SIDIAP) for women. In the oHCM cohort, the percentage of men ranged from 43.04% (SIDIAP) to 60.73% (CPRD-GOLD and InGef RDB) (Table 5), with a median age ranging from 57 years (IQR: 46-65) (CPRD-GOLD) to 68 years (IQR: 59-77) (NAJS) for men and from 67 years (IQR: 57-78) (CPRD-GOLD) to 76 years (IQR: 66-83) (SIDIAP and NAJS) for women.

**Table 5.** Baseline characteristics of study participants by HCM and oHCM cohorts and study database.

| Variable name | Variable level | Estimate name | Study database | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | CPRD GOLD | | DK-DHR | | InGef RDB | | NAJS | | NLHR | | SIDIAP | |
| | | | Cohort name | | | | | | | | | | | |
| | | | HCM | oHCM | HCM | oHCM | HCM | oHCM | HCM | oHCM | HCM | oHCM | HCM | oHCM |
| Number subjects | | N | 1,780 | 1,062 | 4,826 | 1,934 | 6,311 | 2,551 | 6,653 | 1,559 | 7,114 | 2,413 | 13,593 | 2,844 |
| Age | | Median [Q25 - Q75] | 61 [50 - 71] | 61 [50 - 71] | 67 [56 - 77] | 69 [60 - 77] | 66 [54 - 78] | 66 [55 - 78] | 71 [60 - 79] | 72 [63 - 80] | 66 [54 - 75] | 67 [58 - 75] | 73 [61 - 82] | 72 [61 - 81] |
| | | Mean (SD) | 59.58 (15.34) | 59.70 (15.58) | 65.42 (15.37) | 67.44 (13.21) | 65.17 (16.02) | 65.41 (15.49) | 68.20 (15.05) | 70.45 (13.62) | 63.22 (15.81) | 64.95 (14.22) | 70.18 (15.15) | 69.94 (14.83) |
| | | Range | 18 to 95 | 18 to 95 | 18 to 101 | 18 to 99 | 18 to 103 | 18 to 100 | 18 to 103 | 19 to 100 | 18 to 99 | 18 to 97 | 18 to 101 | 18 to 101 |
| Sex | Female | N (%) | 663 (37.25%) | 417 (39.27%) | 2,272 (47.08%) | 1,077 (55.69%) | 2,431 (38.52%) | 1,167 (45.75%) | 3,170 (47.65%) | 772 (49.52%) | 2,861 (40.22%) | 1,163 (48.20%) | 6,159 (45.31%) | 1,620 (56.96%) |
| | Male | N (%) | 1,117 (62.75%) | 645 (60.73%) | 2,554 (52.92%) | 857 (44.31%) | 3,880 (61.48%) | 1,384 (54.25%) | 3,483 (52.35%) | 787 (50.48%) | 4,253 (59.78%) | 1,250 (51.80%) | 7,434 (54.69%) | 1,224 (43.04%) |
| **Predefined comorbidities any time prior to the index date** | | | | | | | | | | | | | | |
| Aberrant premature complexes | | N (%) | 0 (0.00%) | 0 (0.00%) | 118 (2.45%) | 46 (2.38%) | 144 (2.28%) | 49 (1.92%) | 181 (2.72%) | 32 (2.05%) | 212 (2.98%) | 49 (2.03%) | 400 (2.94%) | 60 (2.11%) |
| Atrial fibrillation | | N (%) | 191 (10.73%) | 111 (10.45%) | 241 (4.99%) | 73 (3.77%) | 1,194 (18.92%) | 354 (13.88%) | 642 (9.65%) | 177 (11.35%) | 850 (11.95%) | 216 (8.95%) | 3,325 (24.46%) | 525 (18.46%) |
| Atrioventricular block | | N (%) | 7 (0.39%) | 5 (0.47%) | 177 (3.67%) | 37 (1.91%) | 260 (4.12%) | 92 (3.61%) | 178 (2.68%) | 31 (1.99%) | 337 (4.74%) | 96 (3.98%) | 790 (5.81%) | 144 (5.06%) |
| Cardiac arrhythmia | | N (%) | 282 (15.84%) | 164 (15.44%) | 1,235 (25.59%) | 409 (21.15%) | 1,743 (27.62%) | 564 (22.11%) | 2,579 (38.76%) | 641 (41.12%) | 2,845 (39.99%) | 894 (37.05%) | 5,681 (41.79%) | 983 (34.56%) |
| Chronic kidney disease | | N (%) | 197 (11.07%) | 114 (10.73%) | 217 (4.50%) | 58 (3.00%) | 1,066 (16.89%) | 330 (12.94%) | 700 (10.52%) | 180 (11.55%) | 380 (5.34%) | 136 (5.64%) | 3,327 (24.48%) | 566 (19.90%) |

| Variable name | Variable level | Estimate name | Study database | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | CPRD GOLD | | DK-DHR | | InGef RDB | | NAJS | | NLHR | | SIDIAP | |
| | | | Cohort name | | | | | | | | | | | |
| | | | HCM | oHCM | HCM | oHCM | HCM | oHCM | HCM | oHCM | HCM | oHCM | HCM | oHCM |
| Chronic obstructive pulmonary disease | | N (%) | 92 (5.17%) | 62 (5.84%) | 366 (7.58%) | 158 (8.17%) | 494 (7.83%) | 190 (7.45%) | 1,113 (16.73%) | 314 (20.14%) | 681 (9.57%) | 250 (10.36%) | 2,075 (15.27%) | 327 (11.50%) |
| Coronary arteriosclerosis | | N (%) | 34 (1.91%) | 16 (1.51%) | 286 (5.93%) | 111 (5.74%) | 1,340 (21.23%) | 463 (18.15%) | 376 (5.65%) | 149 (9.56%) | 849 (11.93%) | 299 (12.39%) | 907 (6.67%) | 155 (5.45%) |
| Disorder of lipoprotein and or lipid metabolism | | N (%) | 198 (11.12%) | 119 (11.21%) | 754 (15.62%) | 299 (15.46%) | 1,574 (24.94%) | 558 (21.87%) | 2,711 (40.75%) | 657 (42.14%) | 1,481 (20.82%) | 527 (21.84%) | 6,177 (45.44%) | 1,268 (44.59%) |
| Essential hypertension | | N (%) | 555 (31.18%) | 344 (32.39%) | 93 (1.93%) | 28 (1.45%) | 3,081 (48.82%) | 1,151 (45.12%) | 5,487 (82.47%) | 1,345 (86.27%) | 4,067 (57.17%) | 1,483 (61.46%) | 8,101 (59.60%) | 1,619 (56.93%) |
| Heart failure | | N (%) | 79 (4.44%) | 46 (4.33%) | 669 (13.86%) | 210 (10.86%) | 1,623 (25.72%) | 522 (20.46%) | 1,368 (20.56%) | 361 (23.16%) | 1,695 (23.83%) | 503 (20.85%) | 4,051 (29.80%) | 632 (22.22%) |
| Ischaemic stroke | | N (%) | 84 (4.72%) | 56 (5.27%) | 474 (9.82%) | 176 (9.10%) | 450 (7.13%) | 165 (6.47%) | 601 (9.03%) | 172 (11.03%) | 796 (11.19%) | 272 (11.27%) | 1,374 (10.11%) | 241 (8.47%) |
| Ischemic heart disease | | N (%) | 258 (14.49%) | 161 (15.16%) | 1,253 (25.96%) | 508 (26.27%) | 1,763 (27.94%) | 590 (23.13%) | 2,136 (32.11%) | 570 (36.56%) | 2,103 (29.56%) | 724 (30.00%) | 2,950 (21.70%) | 530 (18.64%) |
| Obesity | | N (%) | 54 (3.03%) | 35 (3.30%) | 368 (7.63%) | 148 (7.65%) | 778 (12.33%) | 272 (10.66%) | 746 (11.21%) | 186 (11.93%) | 501 (7.04%) | 157 (6.51%) | 3,826 (28.15%) | 783 (27.53%) |
| Premature atrial contraction | | N (%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) |
| Sustained ventricular tachycardia | | N (%) | 13 (0.73%) | 5 (0.47%) | 101 (2.09%) | 30 (1.55%) | 162 (2.57%) | 36 (1.41%) | 125 (1.88%) | 40 (2.57%) | 293 (4.12%) | 81 (3.36%) | 182 (1.34%) | 23 (0.81%) |
| Type 2 diabetes mellitus | | N (%) | 159 (8.93%) | 101 (9.51%) | 490 (10.15%) | 182 (9.41%) | 1,004 (15.91%) | 339 (13.29%) | 2,087 (31.37%) | 506 (32.46%) | 747 (10.50%) | 270 (11.19%) | 3,750 (27.59%) | 632 (22.22%) |

| Variable name | Variable level | Estimate name | Study database | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | CPRD GOLD | | DK-DHR | | InGef RDB | | NAJS | | NLHR | | SIDIAP | |
| | | | Cohort name | | | | | | | | | | | |
| | | | HCM | oHCM | HCM | oHCM | HCM | oHCM | HCM | oHCM | HCM | oHCM | HCM | oHCM |
| Valvular heart disease | | N (%) | 112 (6.29%) | 66 (6.21%) | 628 (13.01%) | 379 (19.60%) | 927 (14.69%) | 361 (14.15%) | 947 (14.23%) | 299 (19.18%) | 1,515 (21.30%) | 673 (27.89%) | 3,067 (22.56%) | 699 (24.58%) |
| Ventricular fibrillation | | N (%) | <5 | <5 | 30 (0.62%) | 9 (0.47%) | 30 (0.48%) | 7 (0.27%) | 44 (0.66%) | 16 (1.03%) | 53 (0.75%) | 12 (0.50%) | 30 (0.22%) | 6 (0.21%) |

## 12.2 Main results

The main results are structured according to the study objectives: i) population-level prevalence (objective 1) and ii) patient-level characteristics (objectives 2-3). Results are presented overall and stratified by study cohort, sex, age group, and year of the index date for each database. Key stratified findings are presented in this report for clarity. All stratified results are available in the shiny app P3-C1-018.

### 12.2.1 Population-level prevalence (Objective 1)

**Prevalence of HCM and oHCM**

The prevalence of HCM increased over time across all study databases, with variations in estimates (**Figure 3A)**. CPRD-GOLD reported the lowest prevalence, reaching 0.043% (95%CI: 0.041–0.046) in 2023, while SIDIAP had the highest, peaking at 0.238% (95%CI: 0.234–0.243) in 2019 before declining slightly in 2020–2021. NLHR and DK-DHR showed intermediate prevalence levels, reaching 0.160% (95%CI: 0.156–0.164) and 0.102% (95%CI: 0.099–0.102) in 2023, respectively. Similarly, NAJS had a prevalence of 0.154% (95%CI: 0.151-0.159) in 2024. InGef RDB followed a similar pattern, with prevalence reaching 0.076% (95%CI: 0.074–0.078) in 2023.

The prevalence of oHCM slightly increased over time,  and remained consistently lower, ranging from 0.027% (95%CI: 0.025–0.029) in CPRD-GOLD to 0.069% (95%CI: 0.067–0.072) in NLHR in 2023 (**Figure 3B)**.

**Prevalence of HCM and oHCM by sex**

Across all databases, the prevalence of HCM was generally higher in men than in women, with steeper increases over time in men (**Figure 4A**). However, sex differences were less pronounced among older adults, particularly in the 80+ age group, where women had similar or slightly higher prevalence than men in all databases except SIDIAP (shiny app P3-C1-018).

For oHCM, while prevalence remained higher in men than women, sex differences were smaller compared to the HCM cohort (**Figure 4B**).

**Prevalence of HCM and oHCM by age**

HCM prevalence increased with age across all databases, peaking in the oldest age groups. The highest rates were observed in the 80+ age group across all databases (in CPRD-GOLD until 2015 and NLHR from 2015) (**Figure 5A**). Similar results were found for oHCM (**Figure 5B**).

Sensitivity analyses using point prevalence instead of period prevalence yielded similar results across all databases (shiny app P3-C1-018).

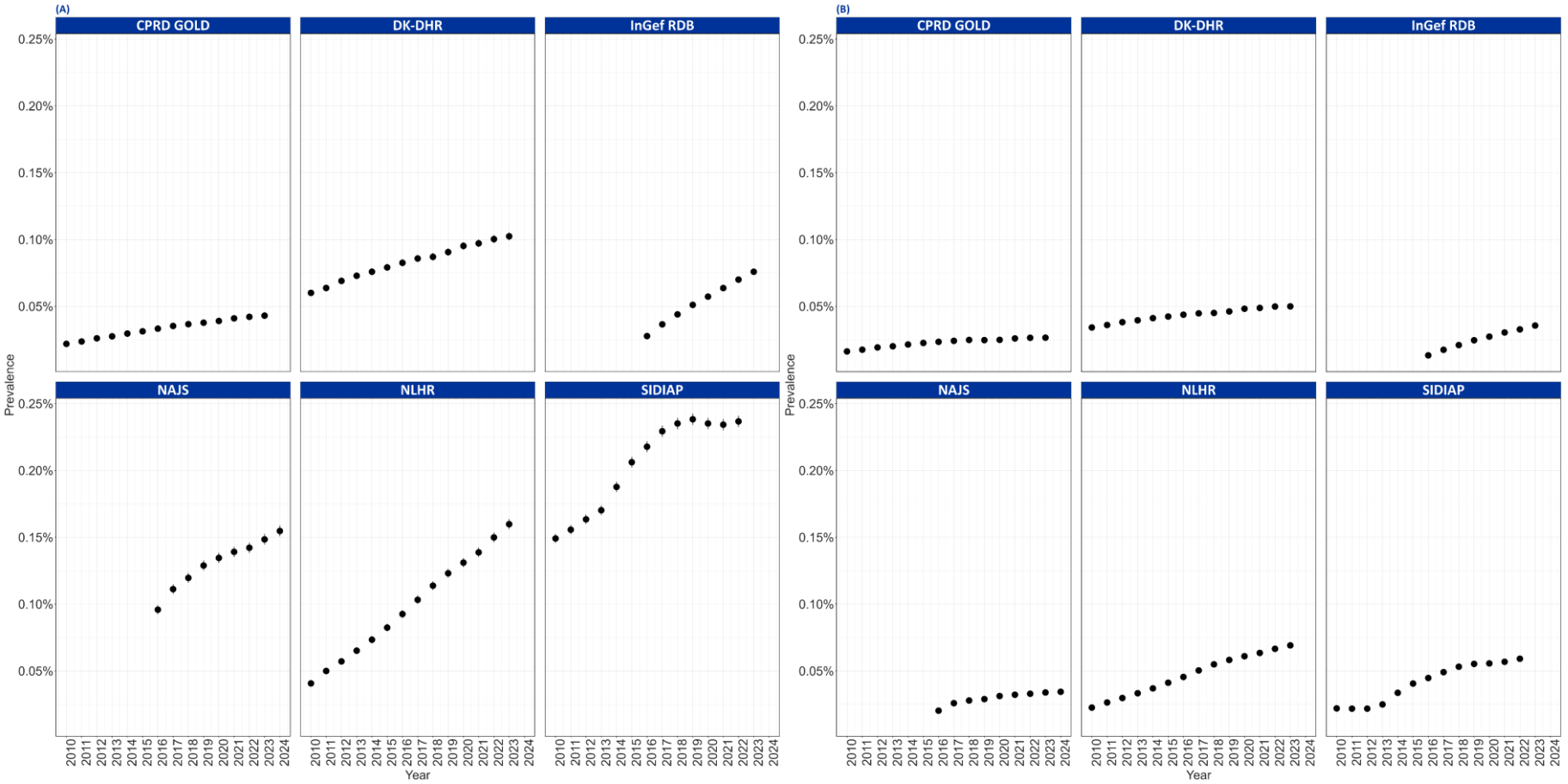



**Figure 3.** Annual period prevalence of HCM (A) and oHCM (B) cohorts by study database

Note: The prevalence estimate for 2015 in NAJS (the earliest available estimate) was excluded, as it was likely inflated, possibly due to all HCM or oHCM diagnoses before 2014 being recorded as starting in 2014 or later.


**Figure 4.** Annual period prevalence of HCM (A) and oHCM (B) cohorts by sex and study database.

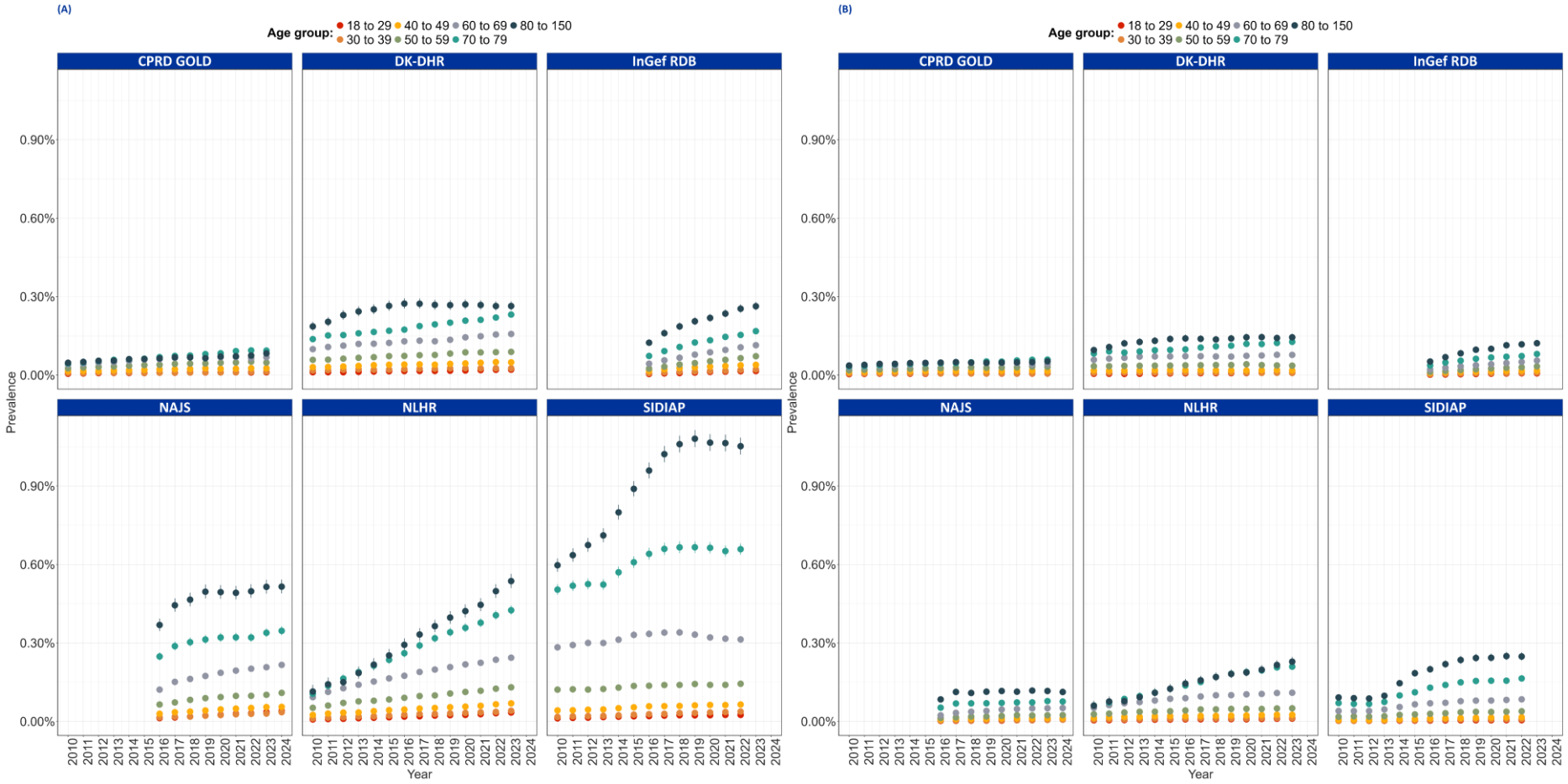



**Figure 5.** Annual period prevalence of HCM (A) and oHCM (B) cohorts by age group and study database

### 12.2.2 Patient-level characteristics (Objectives 2 and 3)

**Figures 6-13** present the frequency of each predefined variable—representing comorbidities, measurements, medications, and procedures—for both the HCM and oHCM cohorts.

It is important to note that when referring to the most common characteristics, this is based on the predefined variables, which were selected for their clinical relevance to HCM based on clinical expertise and previous literature. However, they may not necessarily represent the most frequent variables recorded overall. A broader exploration of the top 50 patient-level concepts can be conducted in the large-scale characteristics tab of the shiny app P3-C1-018.

Across all databases, frequencies consistently increased with age, reflecting the expected higher prevalence of HCM among older age groups and the generally higher rates of morbidity and medication use in these populations (shiny app P3-C1-018).

**Predefined comorbidities**

The most common comorbidities recorded at any time before the index date in individuals with HCM across databases were essential hypertension (31.18% in CPRD-GOLD–82.47% in NAJS), cardiac arrhythmia (15.84% in CPRD-GOLD–41.79% in SIDIAP), ischemic heart disease (14.49% in CPRD-GOLD–32.11% in NAJS), HF (4.44% in CPRD-GOLD–29.80% in SIDIAP), and AF (4.99% in DK-DHR–24.46% in SIDIAP) (Table 5). Notably, DK-DHR reported very low rates of essential hypertension (<2%), suggesting potential underreporting of this condition. This is further supported by the low—mostly zero—counts of essential hypertension among the matched sample from the general population (see section 12.3.2 Other analysis (exploratory)). In the three months before the index date, cardiac arrhythmia (2.64% in CPRD-GOLD–29.08% in NAJS), ischemic heart disease (2.42% in CPRD-GOLD–18.76% in NAJS), and HF (1.01% in CPRD-GOLD–14.59% in NLHR) were among the most frequently recorded comorbidities, remaining the most common comorbidities three months after index date (**Figure 6**). Similar patterns were observed across other time windows before, at, and after the index date, which can be further explored in the shiny app P3-C1-018. Notably, NAJS had a generally higher frequency of comorbidities compared to other databases, particularly for essential hypertension, disorders of lipoprotein and/or lipid metabolism, type 2 diabetes mellitus, ischemic heart disease, and cardiac arrhythmia.. When stratified by sex, the frequency of the most common comorbidities remained similar. However, women had higher frequencies of chronic kidney disease (CPRD-GOLD), HF (SIDIAP), and valvular heart disease (DK-DHR, InGef RDB, SIDIAP), while men had a higher prevalence of cardiac arrhythmia, ischemic heart disease, and coronary arteriosclerosis (NLHR) (**Appendix 1-2**).

Comorbidity patterns in oHCM largely mirrored those observed in HCM, with similar overall frequencies. Essential hypertension, cardiac arrhythmia, ischemic heart disease, and HF were also among the most frequently recorded comorbidities. The prevalence of essential hypertension ranged from 0.85% (CPRD-GOLD) to 69.53% (NAJS), cardiac arrhythmia from 2.54% (CPRD-GOLD) to 31.05% (NAJS), ischemic heart disease from 2.82% (CPRD-GOLD) to 21.87% (NAJS), and HF from 1.04% (CPRD-GOLD) to 14.56% (NAJS), in the three months before the index date (**Figure 7**). However, valvular heart disease was more common in the oHCM cohort than in the HCM cohort, particularly in DK-DHR, InGef RDB, NAJS, NLHR, and SIDIAP.

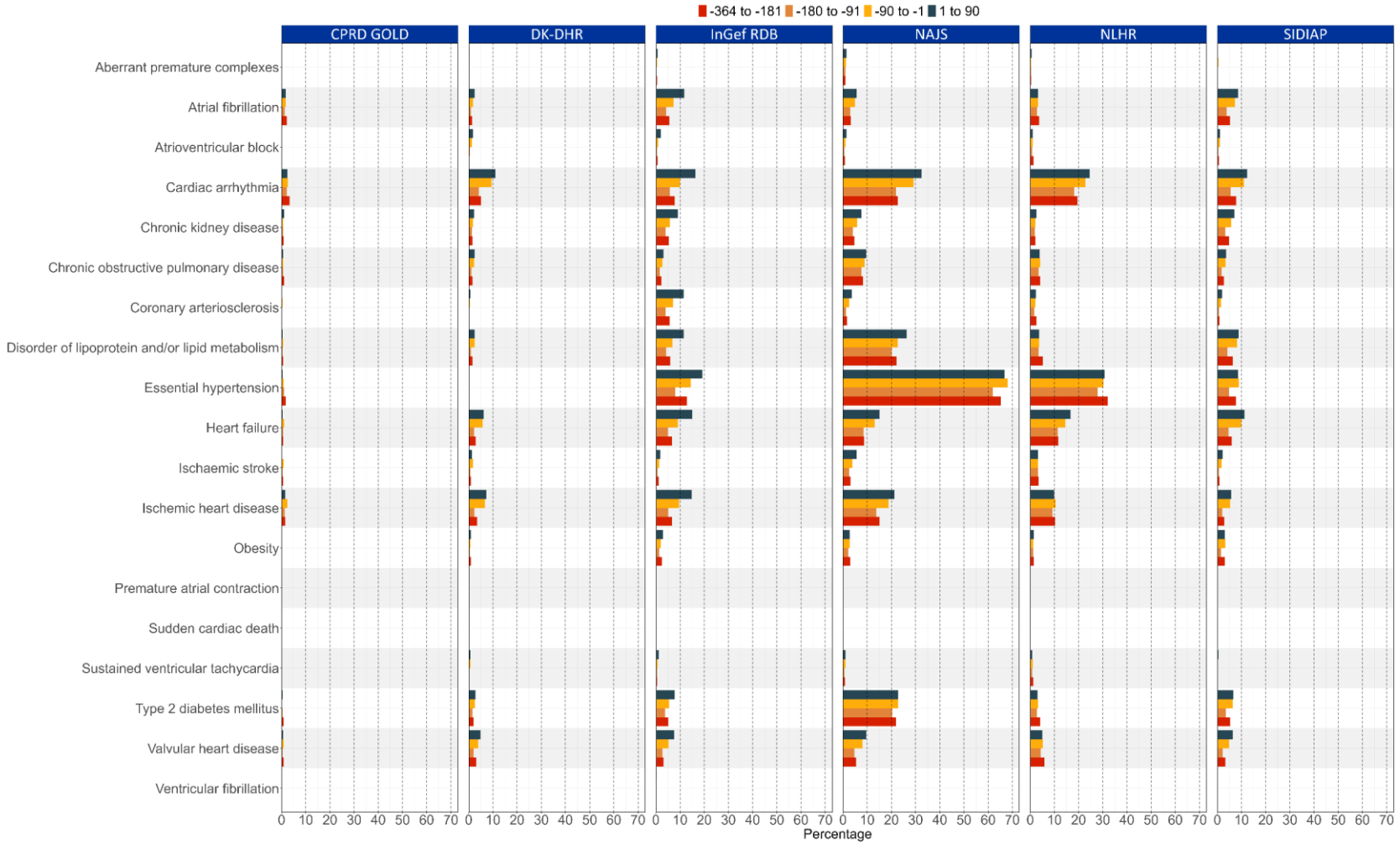



**Figure 6.** Frequency (%) of comorbidities by time window and study database in the HCM cohort

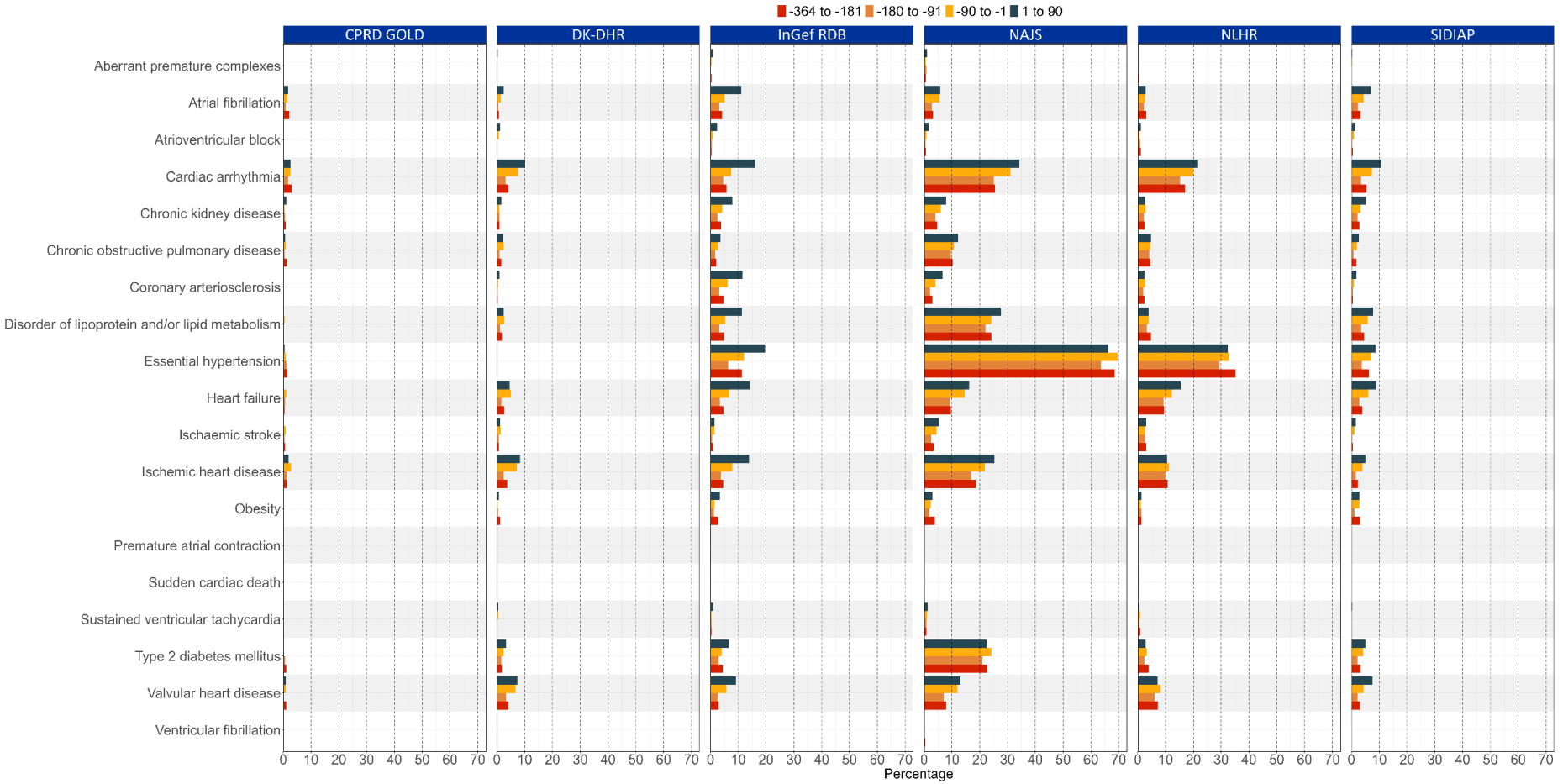



**Figure 7.** Frequency (%) of comorbidities by time window and study database in the oHCM cohort.

**Predefined measurements**

It is worth noting that the results presented below on predefined measurements largely reflect data completeness issues across data sources, rather than clinical differences among patients from different healthcare settings.

Echocardiography was the most frequently recorded measurement across databases, although the frequency varied considerably. In the 90 days prior to the index date, it was most commonly recorded in InGef RDB (21.25%), followed by NAJS (13.20%), SIDIAP (6.04%), and CPRD-GOLD (2.42%) (**Figure 8**). Cardiac catheterisation was the most frequently recorded measurement in the three months before the index date in InGef RDB (33.94%), but its prevalence remained below 5% in NAJS (3.13%) and CPRD-GOLD (0.84%) and was not recorded in other databases. Similarly, cardiac MRI was most commonly reported in InGef RDB (12.36%), along with left ventriculogram (11.04%), but was rarely recorded in other databases. Holter electrocardiogram was most frequently recorded in NAJS (4.57%) but was rarely recorded in other databases. Exercise test and endomyocardial biopsy were recorded only in CPRD-GOLD and InGef RDB at much lower frequencies (<5%). LVEF measurements were only available in SIDIAP (1.61% in the three months before the index date). DK-DHR and NLHR had no available data on measurements, and no data were recorded for LVOT measurements, genetic testing, or heart wall thickness across all databases. No notable differences were observed by sex (**Appendix 1-2**).

For the oHCM cohort, measurement patterns were consistent with those observed in HCM (**Figure 9**).

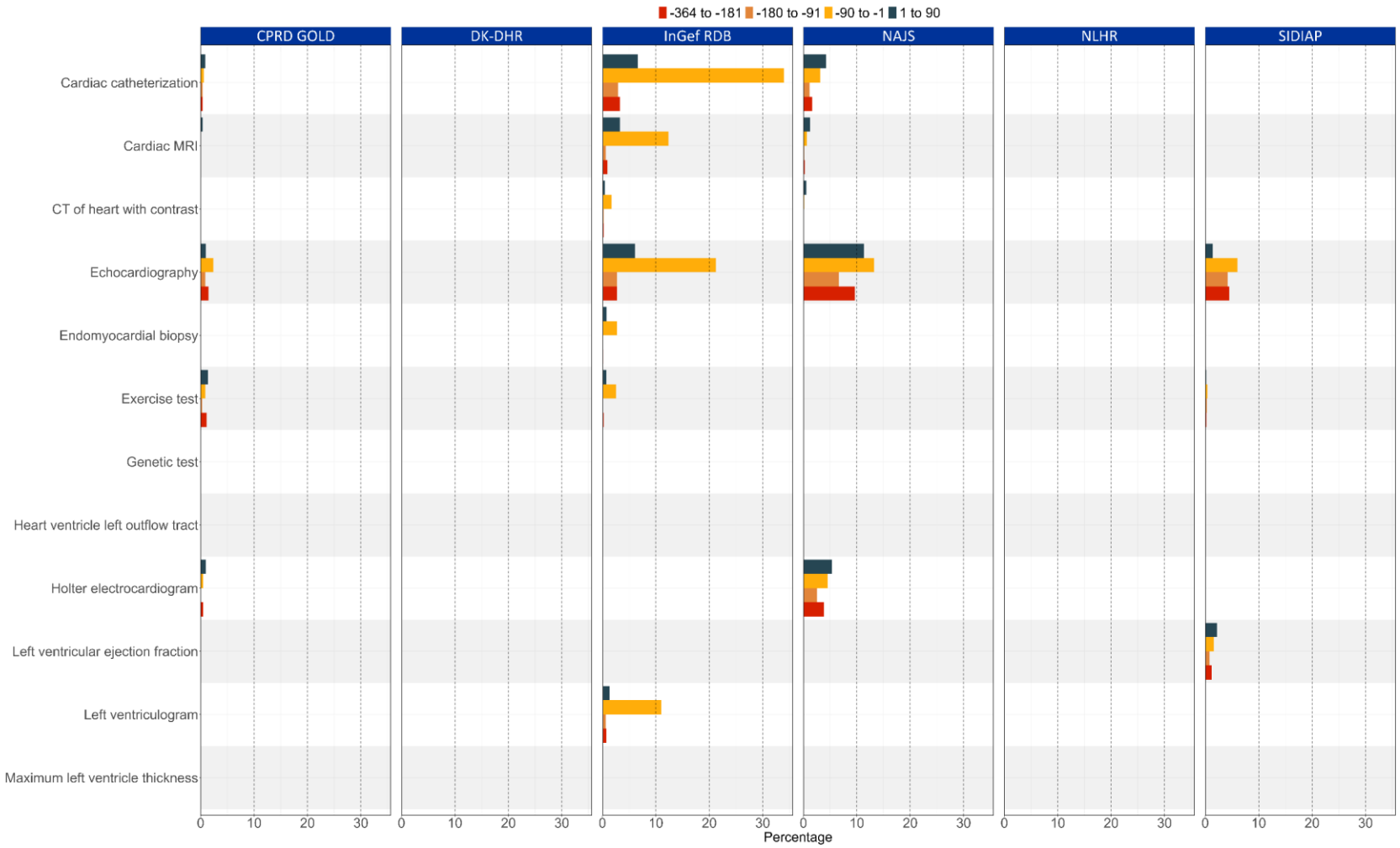



**Figure 8.** Frequency (%) of measurements by time window and study database in the HCM cohort.

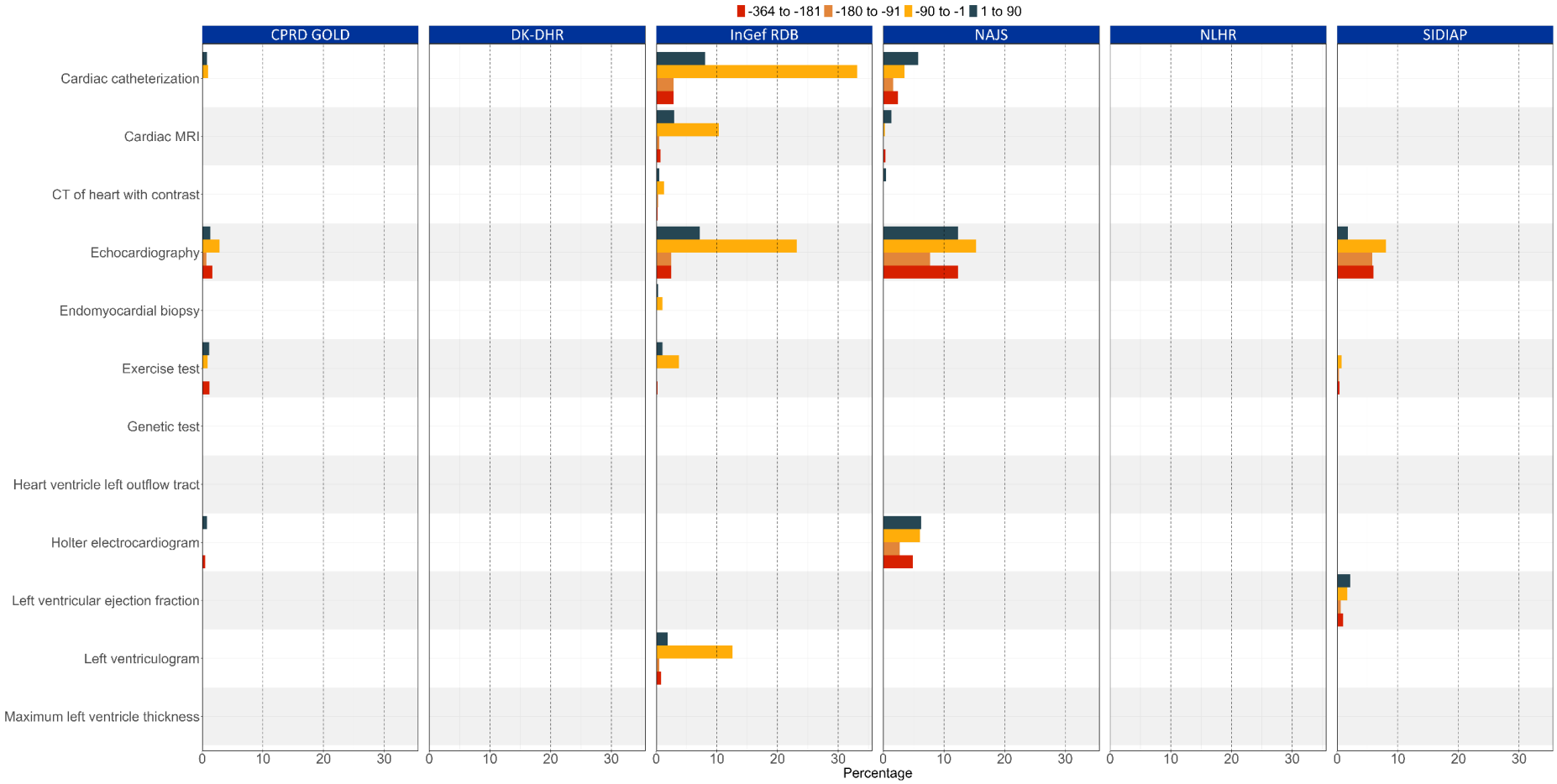



**Figure 9.** Frequency (%) of measurements by time window and study database in the oHCM cohort.

**Predefined medications**

Beta-blocker agents were the most frequently recorded medication, with prevalence ranging from 28.41% (NLHR) to 62.51% (InGef RDB) at any time before the index date (shiny app P3-C1-018), and from 21.49% (DK-DHR) to 47.77% (SIDIAP) in the three months prior (**Figure 10**). Diuretics were also among the three most commonly recorded medications, with prevalence ranging from 15.63% (NLHR) to 59.80% (SIDIAP) at any time before the index date and 12.33% (NLHR) to 42.86% (SIDIAP) in the three months prior to the index date, as well as ACE inhibitors, with frequencies ranging from 11.16% (InGef RDB) to 56.15% (SIDIAP) at any time before the index date and 8.86% (NLHR) to 29.03% (SIDIAP) in the three months prior to the index date. In NLHR, after beta-blockers, angiotensin II receptor blockers and platelet aggregation inhibitors excluding heparin were the most commonly recorded medications at any time before the index date (21.27% and 18.95%, respectively), with similar patterns persisting in the three months prior (18.57% and 15.18%, respectively). These medications remained the most frequently recorded at and after the index date. Vitamin K antagonists were notably common in NAJS and SIDIAP compared to other databases, with over 10% of individuals receiving them before and after the index date. Sex-specific differences were observed in NLHR, where oral anticoagulants were more frequently prescribed among men and beta-blockers among women. Moreover, in NAJS and SIDIAP, diuretics, angiotensin II receptor blockers, selective calcium channel blockers, and digoxin were more frequently prescribed among women, while ACE inhibitors, aldosterone antagonists, and platelet aggregation inhibitors were more common among men (**Appendix 1-2**). Additionally, InGef RDB was the only database to record mavacamten, although the counts were low (0.25% at the index date, peaking at 0.76% five or more years post-index date).

In the oHCM cohort, findings were largely consistent with those observed in the HCM cohort, with beta-blocker agents, ACE inhibitors, and diuretics being the most frequently recorded medications across databases, with frequencies ranging from 33.69% (NLHR) to 66.84% (NAJS), 7.21% (NLHR) to 27.45% (CPRD-GOLD), 11.27% (NLHR) to 60.00% (NAJS), respectively, in the three months post-index date (**Figure 11**). In SIDIAP, selective calcium channel blockers were more commonly prescribed than in the HCM cohort, particularly after the index date. Similarly, in NAJS, diuretics were more frequently prescribed than in the HCM cohort. Mavacamten was also more frequent in the oHCM cohort than in the HCM cohort within InGef RDB, with prevalence more than doubling and peaking at 1.60% five or more years after the index date.

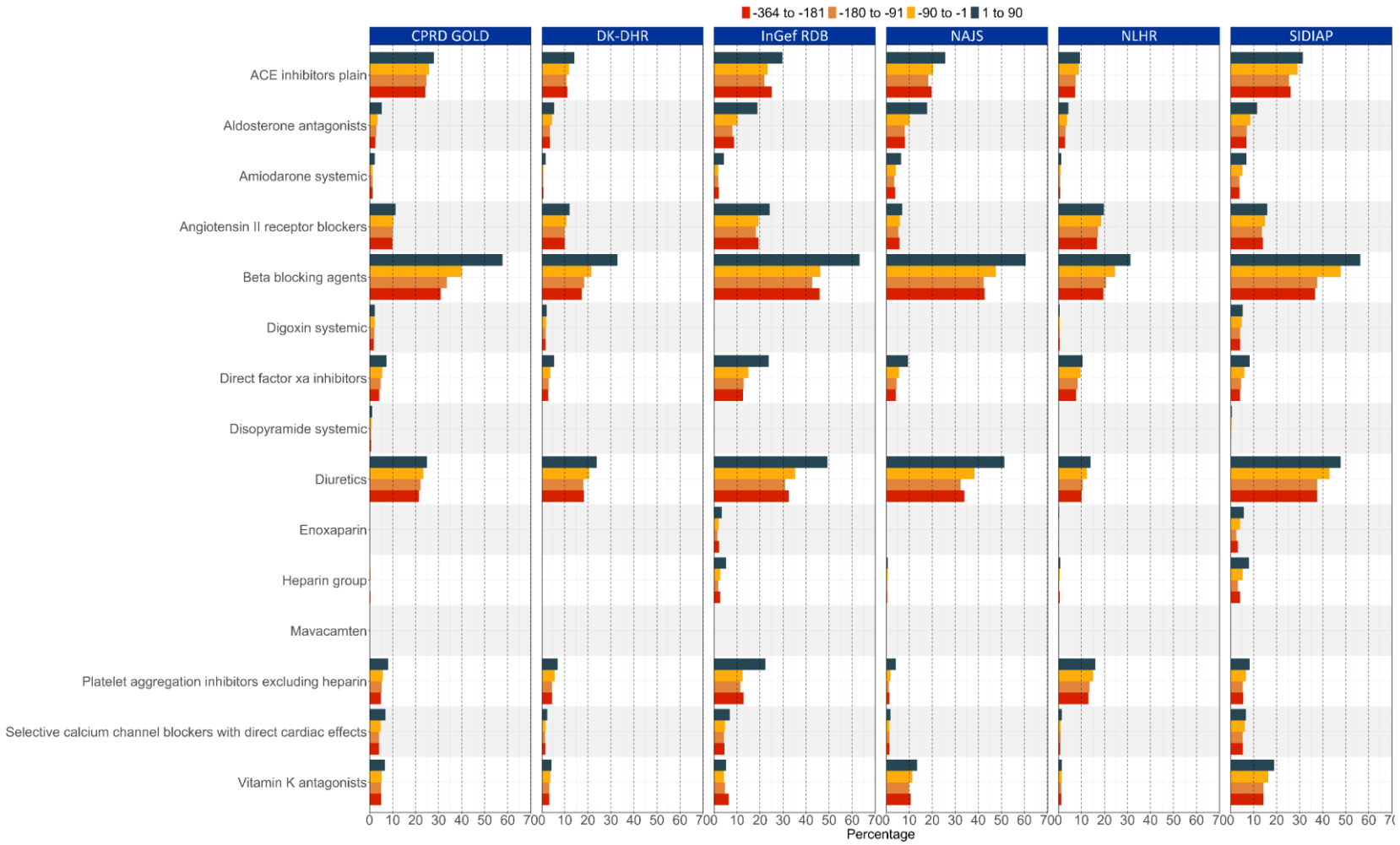



**Figure 10.** Frequency (%) of medications by time window and study database in the HCM cohort.

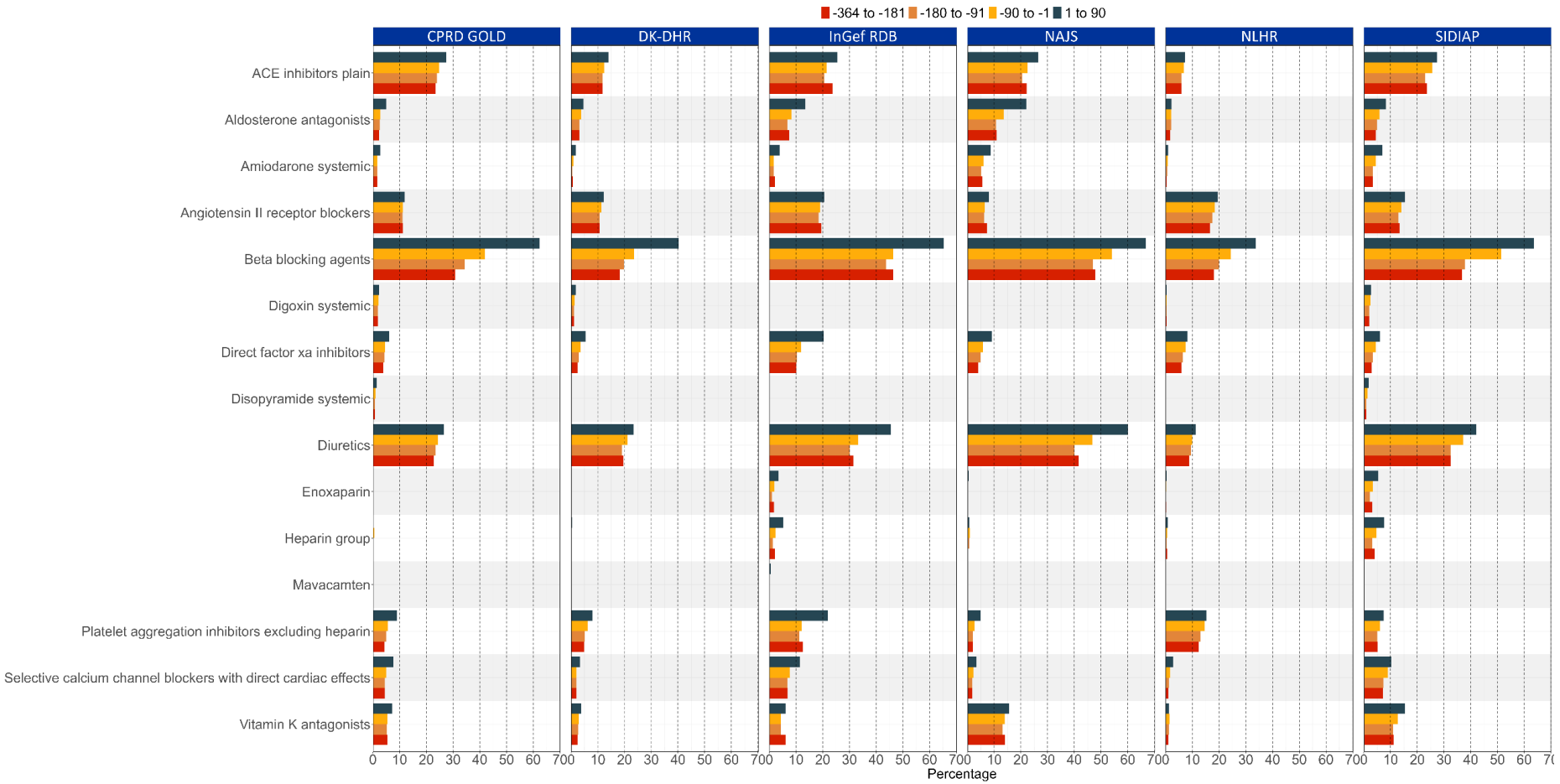



**Figure 11.** Frequency (%) of medications by time window and study database in the oHCM cohort

**Predefined procedures**

The most commonly recorded procedures were pacemaker implantation, defibrillator implantation, and septal reduction therapy, with data available only on CPRD-GOLD, InGef RDB, and NAJS and being most frequently recorded in the InGef RDB, with frequencies of 6.02%, 3.20%, and 1.76%, respectively, in the three months prior to the index date, decreasing to 2.52%, 1.25% and 1.11% in the three months post-index date (**Figure 12**). Defibrillator implantation peaked between one and three years post-index date in InGef RDB (1.63%), and five or more years after the index date in CPRD-GOLD (1.52%) and NAJS (1.44%) (shiny app P3-C1-018). Similarly, pacemaker implantation was most commonly recorded between one and three years post-index date in InGef RDB (3.79%) and NAJS (6.14%), and five or more years post-index date in CPRD-GOLD (2.90%). Heart valve transplantation was recorded in DK-DHR, InGef RDB, NAJS, NLHR, and SIDIAP, with the highest frequencies observed five or more years post-index date (3.82%, 2.86%, 2.36%, 1.17%, and 2.07%, respectively) (shiny app P3-C1-018). Heart transplantation was rarely recorded across databases, with few counts in NAJS and SIDIAP. No notable differences were observed by sex (**Appendix 1-2**).

For the oHCM cohort, procedure patterns were largely consistent with those observed in HCM, though septal reduction therapy was slightly more common in the oHCM cohort (e.g., 4.16% vs. 1.81% in HCM in the three months prior to the index date in InGef RDB) (**Figure 13**). Heart valve transplantation was also more frequent in oHCM (e.g., the proportion of individuals undergoing the procedure doubled five or more years after the index date (6.28%) in DK-DHR) (shiny app P3-C1-018).

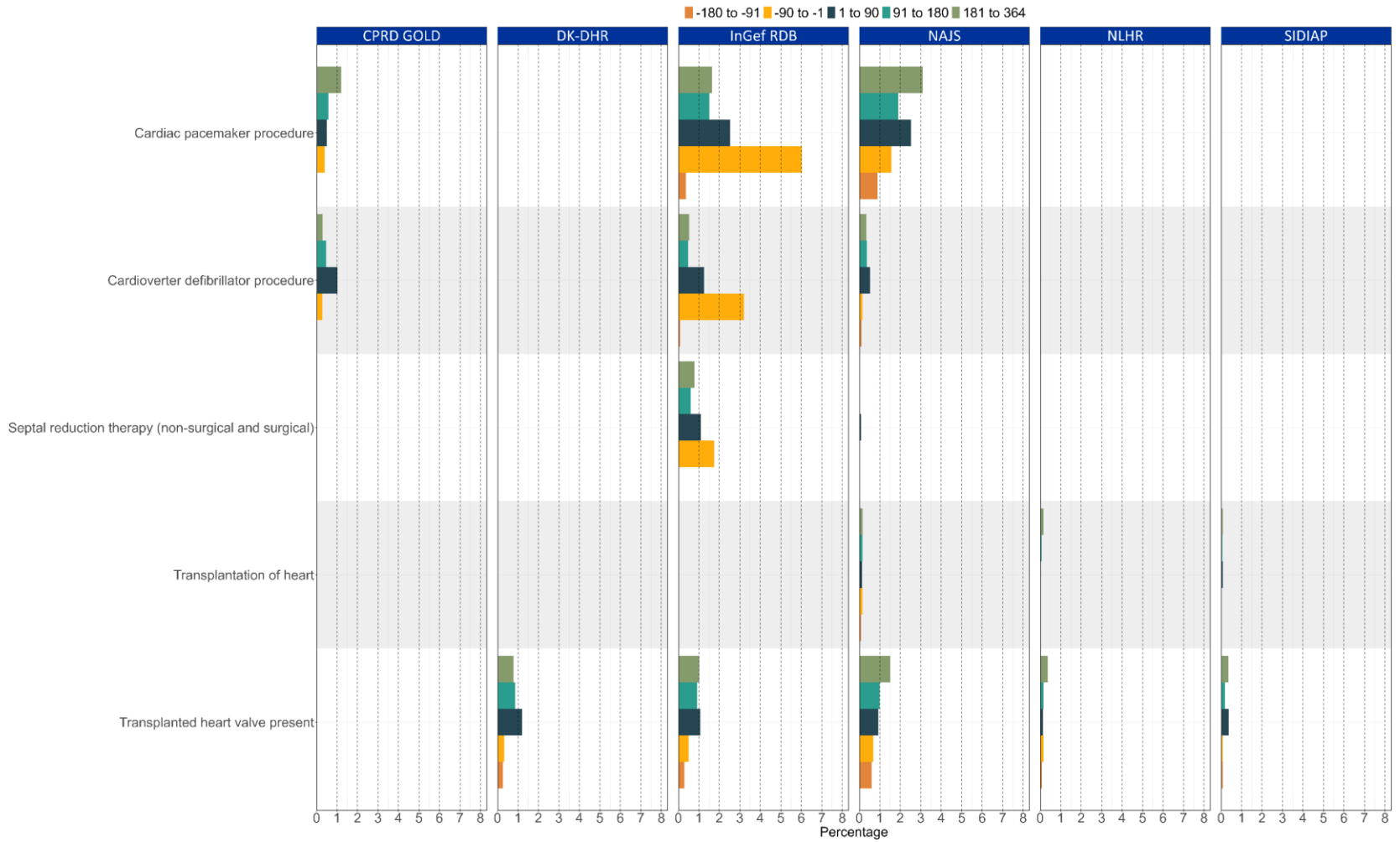



**Figure 12.** Frequency (%) of procedures by time window and study database in the HCM cohort.

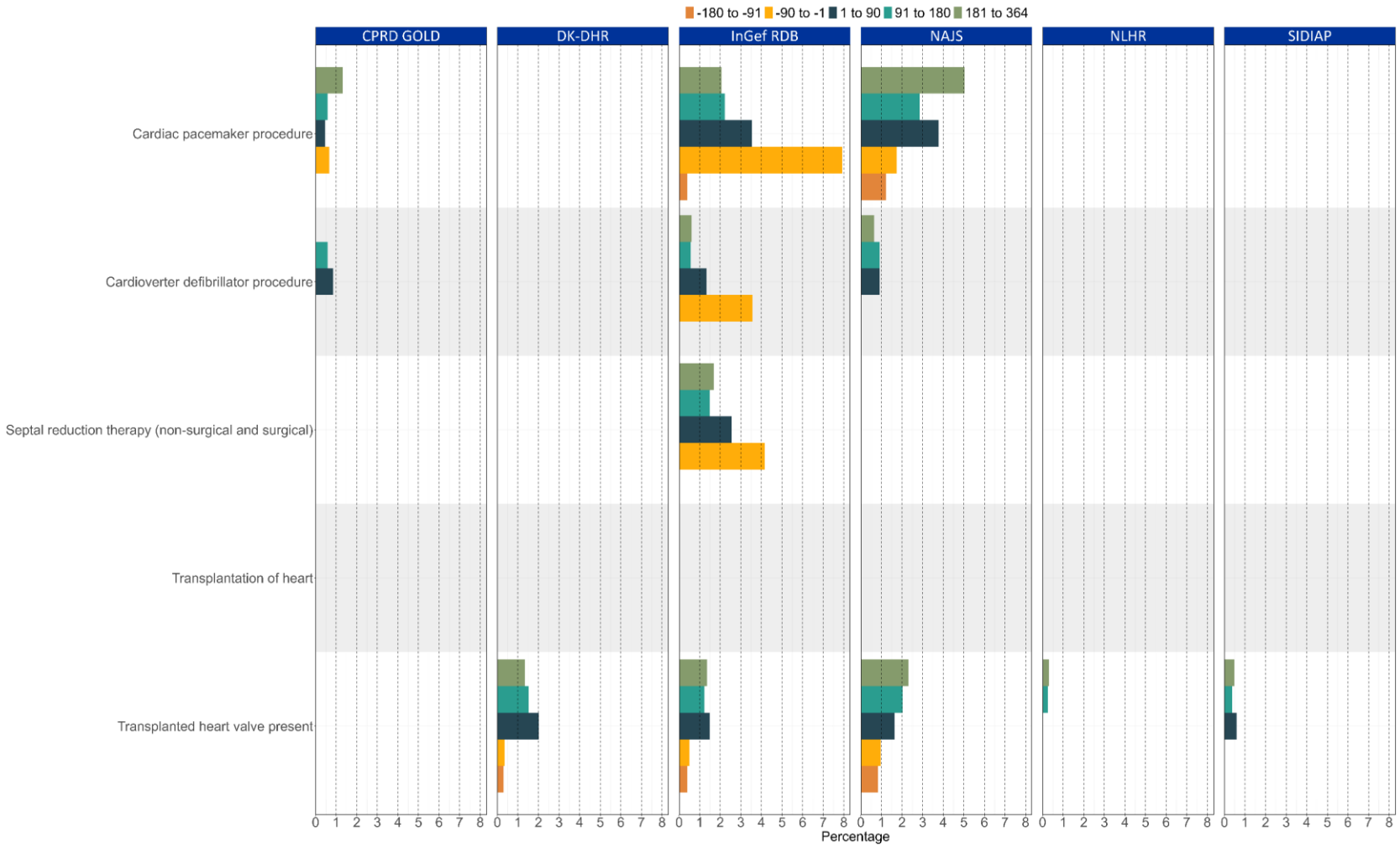



**Figure 13.** Frequency (%) of procedures by time window and study database in the oHCM cohort.

**Stratification by year on diagnosis (index date)**

When stratified by year of index date (before or from 2020 onwards), patterns of comorbidities were largely similar across databases, with some small differences observed in measurements and medications (**Appendix 3-4**). From 2020 onwards, the records of cardiac MRI increased in InGef RDB, and in SIDIAP, echocardiography, LVEF measurements, and exercise tests were more frequently recorded. For medications, in InGef RDB, mavacamten was only recorded among individuals diagnosed from 2020 onwards, aligning with its approval date. In NLHR, medication frequencies were notably lower for individuals with an index date before 2020.

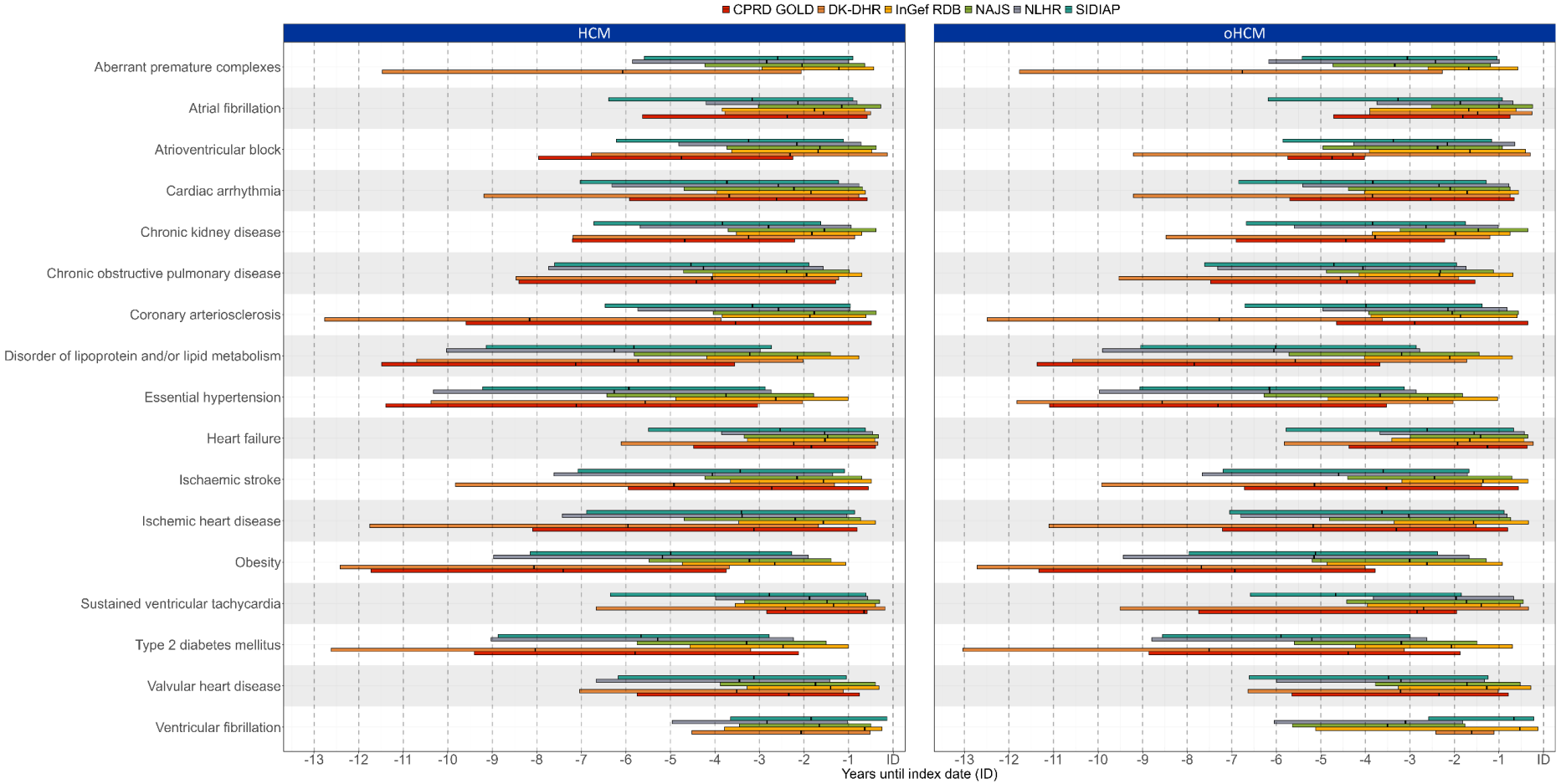
## 12.3 Other analyses (exploratory)

### 12.3.1 Time from first record of comorbidities, measurements, or medications to the index date

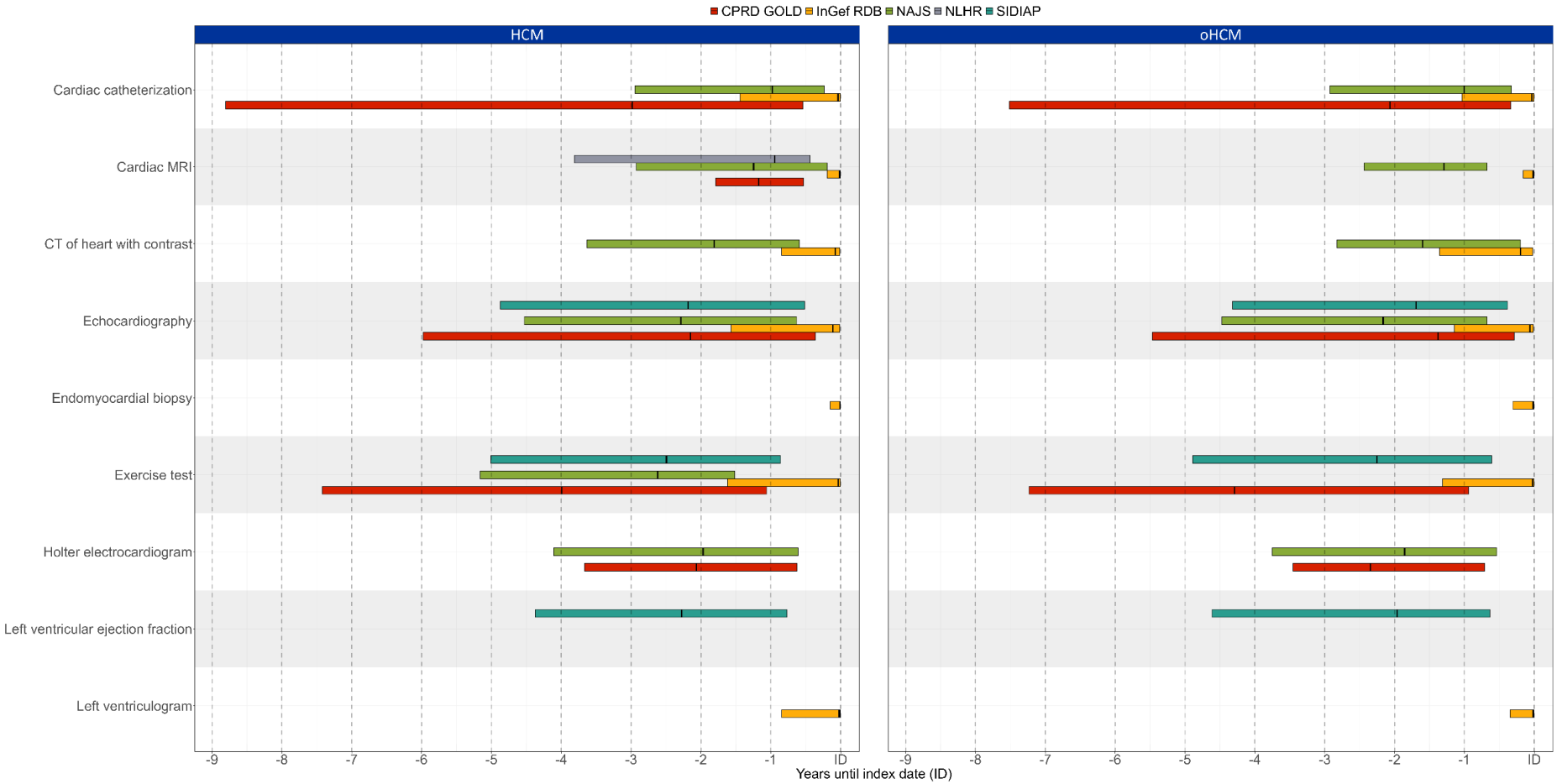
Across databases, most comorbidities, measurements, and medications were first recorded more than one year before the index date in the HCM cohort (**Figure 14**.) However, exceptions were observed for ventricular fibrillation, which had a median time of -238 days (IQR: -1,037 to -215) in CPRD-GOLD, -233 days (IQR: -1,383 to -158) in InGef RDB, and -242 days (IQR: -944 to -79) in SIDIAP. Additionally, InGef RDB differed from other databases in that most measurements were first recorded within the month before the index date.

Similarly, in the oHCM cohort, most comorbidities, measurements, and medications were also first recorded more than one year before the index date, except for disopyramide treatment in SIDIAP, with a median time of -306 days (IQR: -935 to -78).

## (A) Comorbidities




## (B) Measurements




## (C) Medications

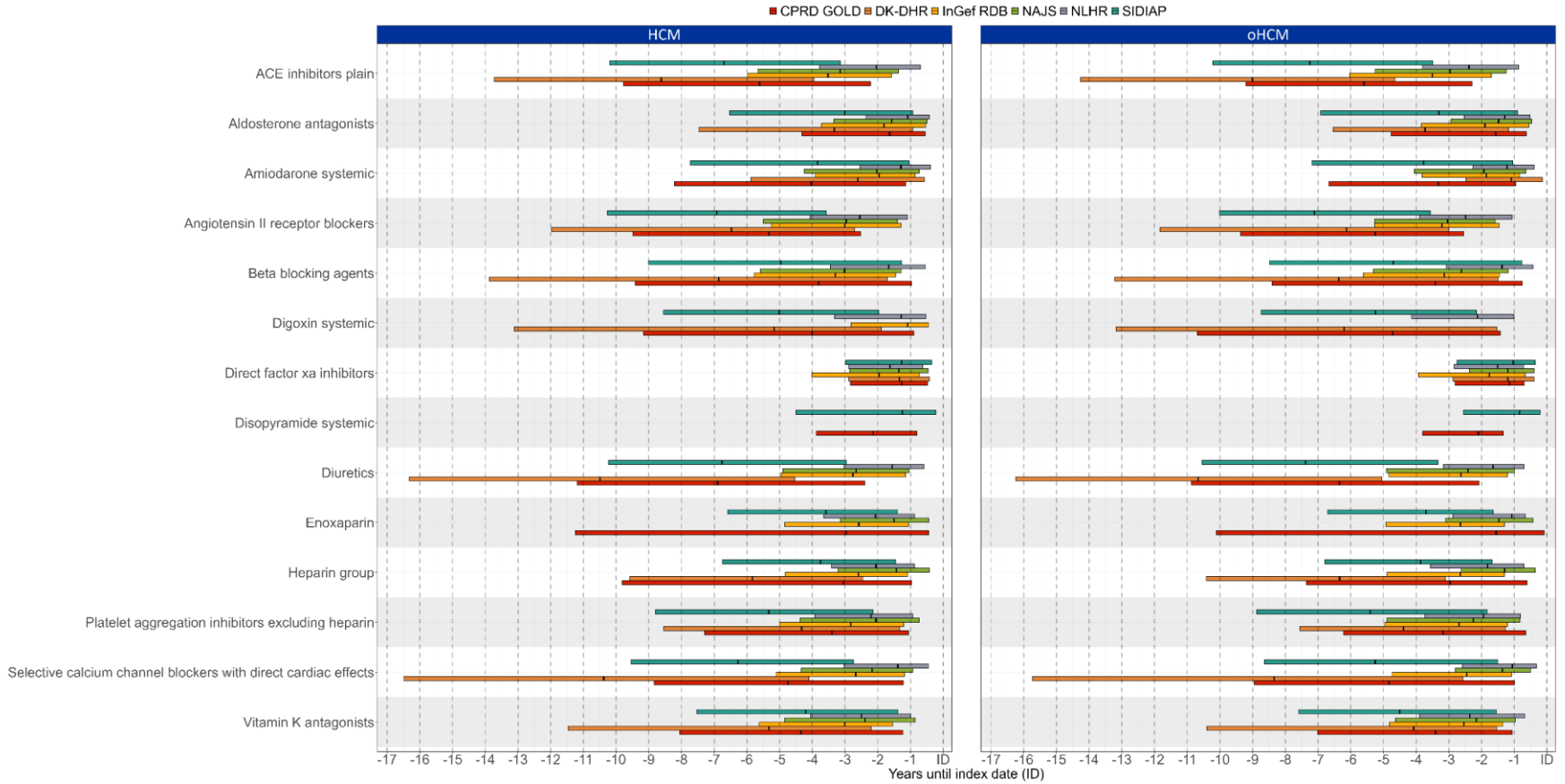



**Figure 14.** Median and interquartile range for time (in days) from the first record of comorbidities (A), measurements (B), and medications (C) to the index date in the HCM and oHCM cohorts.

### 12.3.2 Comparison with an age- and sex-matched general population sample

Across all study databases, most predefined HCM-related comorbidities, measurements, medications, and procedures were more frequent in the study cohort than in the matched general population (**Appendix 5)**. These findings further support the robustness of the phenotyping process, suggesting that the study population has been accurately identified.

# 13. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

Adverse events/adverse reactions were not collected or analysed as part of this evaluation. The nature of this non-interventional evaluation, through the use of secondary data, does not fulfil the criteria for reporting adverse events, according to module VI, VI.C.1.2.1.2 of the Good Pharmacovigilance Practices (https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/guideline-goodpharmacovigilance-practices-gvp-module-vi-collection-management-submission-reports_en.pdf).

# 14. DISCUSSION

## 14.1 Key results

A total of over 40,200 individuals with HCM were identified across all study databases, with cohort sizes varying between them. The proportion of individuals with oHCM was highest in CPRD-GOLD (60%) and lowest in SIDIAP (21%). At date of index date (hereinafter refer to as the date of first recorded HCM or oHCM diagnosis), women were consistently older than men across all databases, with median ages ranging from 70 to 73 years for women compared to 61-65 years for men. In CPRD-GOLD, individuals had a first recorded diagnosis at a younger age compared to the other databases, with median ages of 67 years for women and 57 years for men.

Overall, prevalence increased over time across all databases. The most recent estimates ranged from 0.04% in CPRD-GOLD (2023) to 0.24% in SIDIAP (2022). CPRD-GOLD had the lowest prevalence and the least pronounced increase over time. Unlike the other databases, SIDIAP showed a slight decline in prevalence in 2020-2021. Similarly, the prevalence of oHCM increased over time but remained consistently lower than that of HCM, ranging from 0.03% in CPRD-GOLD to 0.07% in NLHR. Prevalence increased with age, with the highest rates observed in the oldest age groups. Additionally, while men generally had higher prevalence rates, older women (80+ years) had similar or even higher prevalence rates than men in most databases. For oHCM, sex differences in prevalence were less pronounced than for HCM.

Cardiovascular conditions were highly prevalent among individuals with HCM and oHCM, with essential hypertension, cardiac arrhythmias (including AF), ischemic heart disease, and HF being the most common comorbidities. Women had higher frequencies of chronic kidney disease in CPRD-GOLD, HF in SIDIAP, and valvular heart disease in DK-DHR, InGef RDB, and SIDIAP. In contrast, men had higher frequencies of cardiac arrhythmias, ischemic heart disease, and coronary arteriosclerosis in NLHR. Moreover, valvular heart disease was more prevalent in oHCM cases in most databases. In terms of medications, beta-blocker agents, diuretics, and ACE inhibitors, were among the most recorded medications for HCM and oHCM. InGef RDB uniquely captured the use of the novel drug mavacamten, which was more frequently to individuals with oHCM, in line with current guidelines. Lastly, most comorbidities and medications were frequently recorded before the first diagnosis of HCM or oHCM, with the first recorded comorbidity or treatment occurring more than a year before.

## 14.2 Limitations of the research methods

This study relied on routinely collected healthcare data, which have inherent limitations, as these data are primarily collected for clinical rather than research purposes.

The first limitation concerns the identification of HCM cases, which varied across databases. This variation is likely due to differences in data sources (whether the data come from primary care only, hospital data only, or a combination of primary and secondary care) and coding practices.. These factors made direct comparisons across databases challenging. Additionally, while false positives (individuals recorded with the condition but who do not truly have it) were expected to be relatively rare, false negatives (individuals with the condition who were not recorded) were likely more frequent, particularly in databases without linkage between primary and secondary care, such as CPRD-GOLD. To minimise this limitation and maximise case identification, a phenotype of HCM and its variant, oHCM, was used. A second strategy was to use predominantly database where we would expect full capture either nationwide registries such as DK-DHR and NLHR, national claims data or databases with primary and secondary care linkage (SIDIAP). Furthermore, since HCM is known to be underdiagnoseddue to many individuals being asymptomatic or experiencing only mild symptoms, delayed diagnoses or undetected cases are likely. This is not possible to mitigate, consequently, this study only captured individuals with clinically recognised HCM, excluding those who remained undiagnosed.

A second limitation relates to missing data, which made it difficult to determine whether the absence of certain variables reflected their true absence or simply a lack of recording. Measurement data were generally underreported across most databases with significant gaps in confirmatory diagnostics measurements, such as heart wall thickness, genetic testing, and LVEF or LVOT assessments. The diagnostic approach for HCM has evolved significantly over recent decades, from simple echocardiographic evaluations to a complex, multimodal strategy incorporating advanced imaging, genetic testing, and biomarker studies. It remains unclear whether the lack of data on these measurements reflects their non-utilisation, suggesting potential gaps in diagnostic practices, or simply underreporting. Similarly, recording of procedures were generally sparse across databases and this is a known limitation of these data sources.

A third limitation concerns the variability in comorbidity prevalence across databases. This heterogeneity can be partly attributed to demographic differences between data sources—for instance, NAJS, which had an overall higher frequency of comorbidities over time, included older individuals compared to CPRD GOLD, where the populations were younger and had a higher proportion of men. In addition, differences in recording practices may have contributed to this variability. For example, NAJS likely captures repeated entries of the same condition (e.g., hypertension) at each patient visit, serving as a proxy for healthcare encounter frequency. In contrast, databases such as CPRD GOLD or DK-DHR may document comorbidities only once, typically at diagnosis.

A fourth limitation is the heterogeneity in HCM and oHCM prevalence observed across databases. These differences likely stem from a range of factors, including variation in demographic characteristics and coding behaviours, as previously mentioned, as well as differences in healthcare system structure and diagnostic practices over time.

Finally, unrelated to the limitations of routinely collected healthcare data, the COVID-19 pandemic (2020–2022) introduced additional challenges by altering healthcare utilisation patterns, routine clinical practices, and data recording. These disruptions may have impacted the identification and reporting of HCM and oHCM during this period, potentially distorting estimates for 2020 and 2021. However, a noticeable impact was observed only in SIDIAP, where a slight decrease in HCM prevalence was recorded in 2020-2021.

## 14.3 Interpretation

Understanding the true prevalence of HCM in the general population has significant implications for clinical practice, disease management, and the evaluation of novel therapies such as mavacamten. Since the first

study published in 1995 (CARDIA), which estimated HCM prevalence at approximately 1 in 500 (0.2%) based on left ventricular hypertrophy identified through imaging,(9) several studies have used different methodologies to assess the frequency of the disease in the general population.(31) While billing and EHR data provide insights into clinical recognition and genomic data help identify at-risk populations, only imaging can establish a clinical diagnosis of HCM with certainty.(31) In this study, using claims, registries and EHR data from multiple European countries, prevalence estimates ranged from 0.04% (CPRD-GOLD) to 0.24%, (SIDIAP). CPRD-GOLD, a primary care database, reported prevalence estimates similar to previous studies using EHR, such as a German study estimating 0.07% in 2015 (3) and studies from the UK and Sweden reporting 0.04%.(32,33) In contrast, the higher prevalence observed in SIDIAP more closely aligns with imaging- and genetic-based studies with prevalences ranging from 0.11 in the UK to 1.4% in the U.S.(11,34) Additionally, is important to mention that the study conducted in Germany, which also used InGef RDB data, reported slightly higher prevalences that our study.(3) Although both studies observed a consistent yearly increase, their HCM prevalence in 2015 was 0.07%, while our first available estimate in 2016 was lower at 0.03%, rising to 0.08% in 2023. Despite using the same case definition, which excluded other conditions that can mimic genetic forms of HCM, the lower estimates in our study may be due to the restriction of requiring data availability in the previous 365 days, a criterion not applied in the German study.

The increasing prevalence observed over time aligns with findings from other studies (3,35) and likely reflects improvements in diagnostic capabilities rather than a true rise in disease incidence. Advances in diagnostic tools, particularly the growing use of cardiac MRI, have contributed to a higher detection rate of HCM.(36) However, in this study, MRI data were only available for InGef RDB, preventing us from directly associating the increase in prevalence with advancements in imaging performance. In addition, increased awareness among clinicians, improved disease management strategies that potentially increase the survival of individuals with HCM, and the visibility of patient advocacy organizations and educational campaigns may have also contributed to the reported rise in prevalence over time.(36)

Our findings regarding age distribution and sex were consistent with those from previous studies.(3,18,33,37–40) HCM prevalence increased with age, with the median age at first recorded diagnosis in the sixties. Overall, men had higher prevalence rates of HCM than women across databases; however, older women had similar or even higher prevalence rates than their male counterparts. For oHCM, sex differences in prevalence were smaller, with women even slightly outnumbering men in one database. Additionally, women tended to be older at the first recorded diagnosis and experienced a higher risk of HF and valvular disease in some databases, consistent with previously described sex differences in HCM.(12,18,41) This might suggest that HCM is often underdiagnosed or diagnosed later in women compared to men, with HCM progressing to the obstructive form before diagnosis, or that women experience a higher progression from non-obstructive HCM to obstructive HCM. Alternatively, it may reflect longer survival in women, as women generally live longer than men, which could result in a larger proportion of women surviving to the later stages of the disease. However, existing evidence showed worse overall survival among women with HCM, which does not support this last hypothesis.(42) These findings reinforce that, despite advances in medical knowledge and technology, sex-related biases may persist in HCM, potentially leading to delayed diagnoses and underutilisation of specialised treatment for women.(43,44)

Similarly, the most common HCM-related comorbidities (essential hypertension, cardiac arrhythmias, ischaemic heart disease, and HF) and medications (beta-blocker agents, diuretics, and ACE inhibitors) identified among individuals with HCM in our study were consistent with those observed in other studies.(3,18,33,45) It is worth highlighting that most of these characteristics were consistently first recorded over a year before the first recorded HCM diagnosis. This suggests that HCM is often diagnosed after a prolonged period of experiencing symptoms or comorbidities, illustrating opportunities for earlier diagnosis, which has been suggested by other study.(17) Alternatively, it may indicate misclassification of the index date, with the condition being recorded consistently after the actual date of diagnosis, particularly in databases that rely solely on primary care data, such as CPRD-GOLD. Two UK studies also

found that HCM-related comorbidities and treatments were already present within the year preceding diagnosis. One study reported stable angina (24.3%), AF (16.1%), and HF (12.8%) as the most common comorbidities, with 53.9% receiving blood pressure-lowering medication, 17.8% of patients on statins, 9.0% receiving anticoagulants, and 8.7% treated with amiodarone.(32) The other study reported hypertension (53.6%), coronary artery disease (30.2%), AF (26.1%), and valvular heart disease (17.0%), with 5.3% of patients having an implantable cardioverter-defibrillator and 7.3% a pacemaker.(17) In contrast, InGef RDB, which included only hospital data, had most measurements first recorded within the month prior to index date, suggesting that hospital data may accurately capture the actual date of HCM diagnosis. InGef RDB also showed higher frequencies of HCM-related comorbidities at the index date, which may be due to the fact that past diagnosis are recorded at the date of hospital admission, or it may reflect a greater representation of individuals with more severe disease at time of diagnosis.(32)

Essential hypertension, which we found to be the most common comorbidity and was highly prevalent before the first recorded HCM or oHCM diagnosis, has previously been described in patients with HCM, with proportions ranging from 31.2% to 82.5%.(3,45–47) Traditionally, the coexistence of hypertension with HCM has not been widely accepted, as hypertension is known to also cause left ventricular hypertrophy. As a result, hypertension has been associated with a delayed diagnosis of HCM,(48) and some studies estimating the prevalence of HCM have even excluded individuals with essential hypertension from their HCM cohorts due to its potential confounding role.(31) A better understanding of the coexistence of these conditions is needed.

The introduction of mavacamten, the first HCM-specific drug, marks a significant advancement in treatment. However, pivotal clinical trials reported AF-related adverse events in 2% to 7% of patients, some of which led to a rapid decline in systolic function and required discontinuation of the drug.(49) Thus, understanding baseline data on comorbidities such as AF in individuals with HCM is essential for informing optimal strategies for arrhythmia monitoring and ensuring treatment safety in real-world settings.

The insights from this study could help in the planning and assessment of future clinical research in this field, in particular by increasing the understanding of the population of patients with HCM and oHCM, including its prevalence, comorbidities, concurrent treatments, and differences by sex.

## 14.4 Generalisability

While our study includes data from six European countries and covers a wide range of healthcare settings (hospital inpatient and outpatient care, secondary care outpatient settings, and primary care databases), caution should be applied when we generalise beyond the specific regions and settings covered by the respective databases.

A key challenge in assessing the prevalence of HCM is the heterogeneous nature of the disease and its well-recognised incomplete phenotypic penetrance. As a result, case identification largely depends on the diagnostic methods used, such as electrocardiography, cardiac MRI, or genetic screening. Variations in diagnostic approaches across settings and applied at population level may influence prevalence estimates and patient characterisation.

Nonetheless, to our knowledge, this is the largest epidemiological study to simultaneously report on the prevalence and characteristics of newly diagnosed HCM patients across six European databases, providing a broader perspective on the disease. Future research expanding this analysis to additional databases could further elucidate differences in HCM prevalence and improve the availability of data on diagnostic measurements, treatment procedures, and emerging treatments such as mavacamten.

# 15. CONCLUSIONS

This large epidemiological study across six European countries identified a consistent yearly increase in the prevalence of clinically recognised HCM. Prevalence was higher among men, although women were older

at first recorded diagnosis, suggesting potential delays in diagnosis among them. Essential hypertension, cardiac arrhythmia, ischaemic heart disease, and HF were the most frequently recorded cardiovascular comorbidities and beta-blockers, diuretics, and ACE inhibitors were among the most commonly prescribed medications for both, HCM and oHCM patients.

Notable variability in the prevalence of HCM, as well as in the frequency of comorbidities, diagnostic measurements, and treatments, was observed across databases, reflecting differences in healthcare settings and data collection methods. Furthermore, the high frequency of cardiovascular comorbidities and HCM-related treatments consistently first recorded more than one year before the index date suggests that HCM may often be diagnosed at a later stage of disease progression.

These findings enhance our understanding of the burden of this genetic heart disease on healthcare systems across Europe and underscore the ongoing need for increased diagnostic awareness among clinicians to ensure timely diagnosis. The results may help inform the development and evaluation of future screening and management strategies, including the introduction of emerging treatments such as mavacamten.

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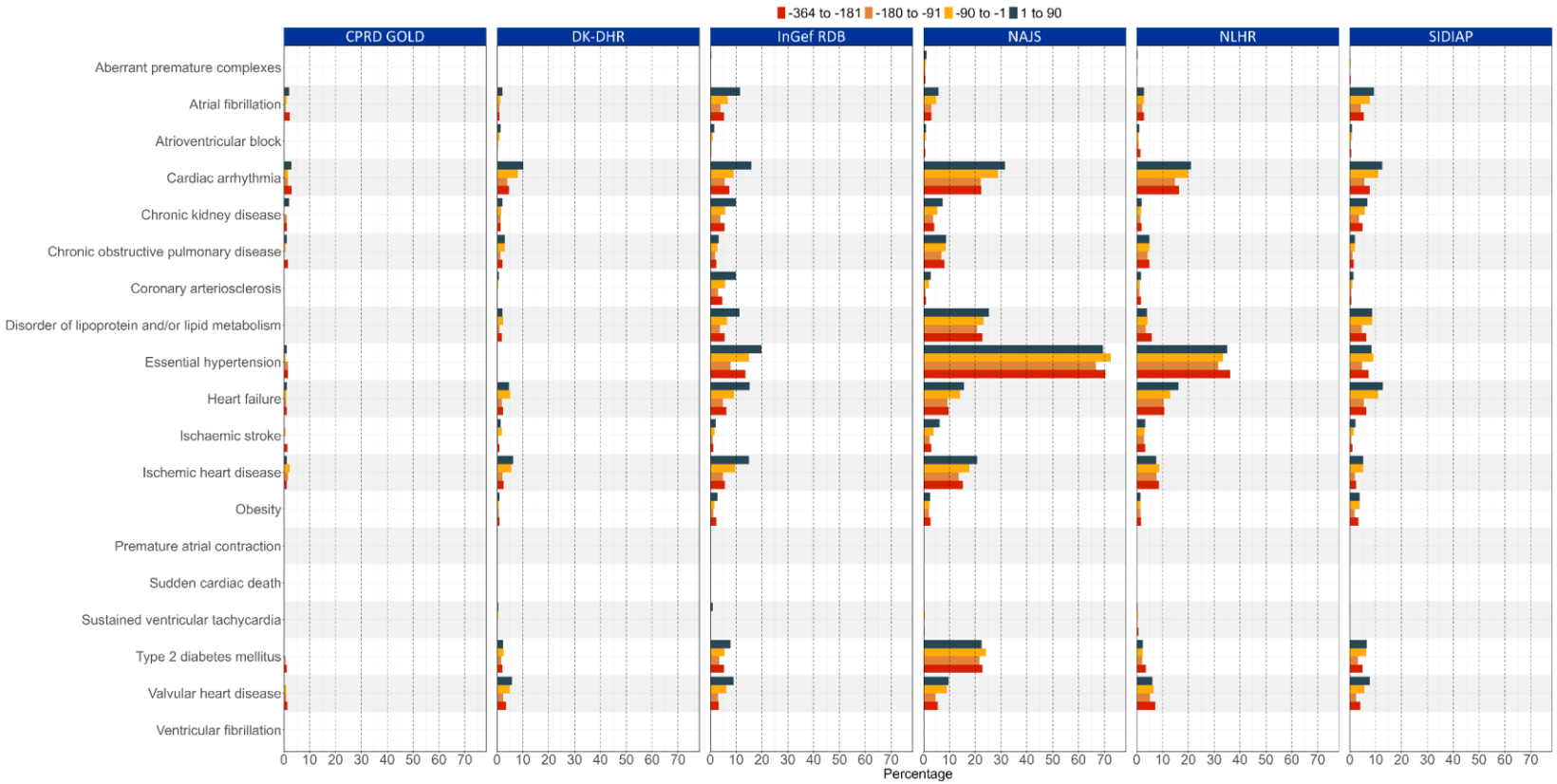
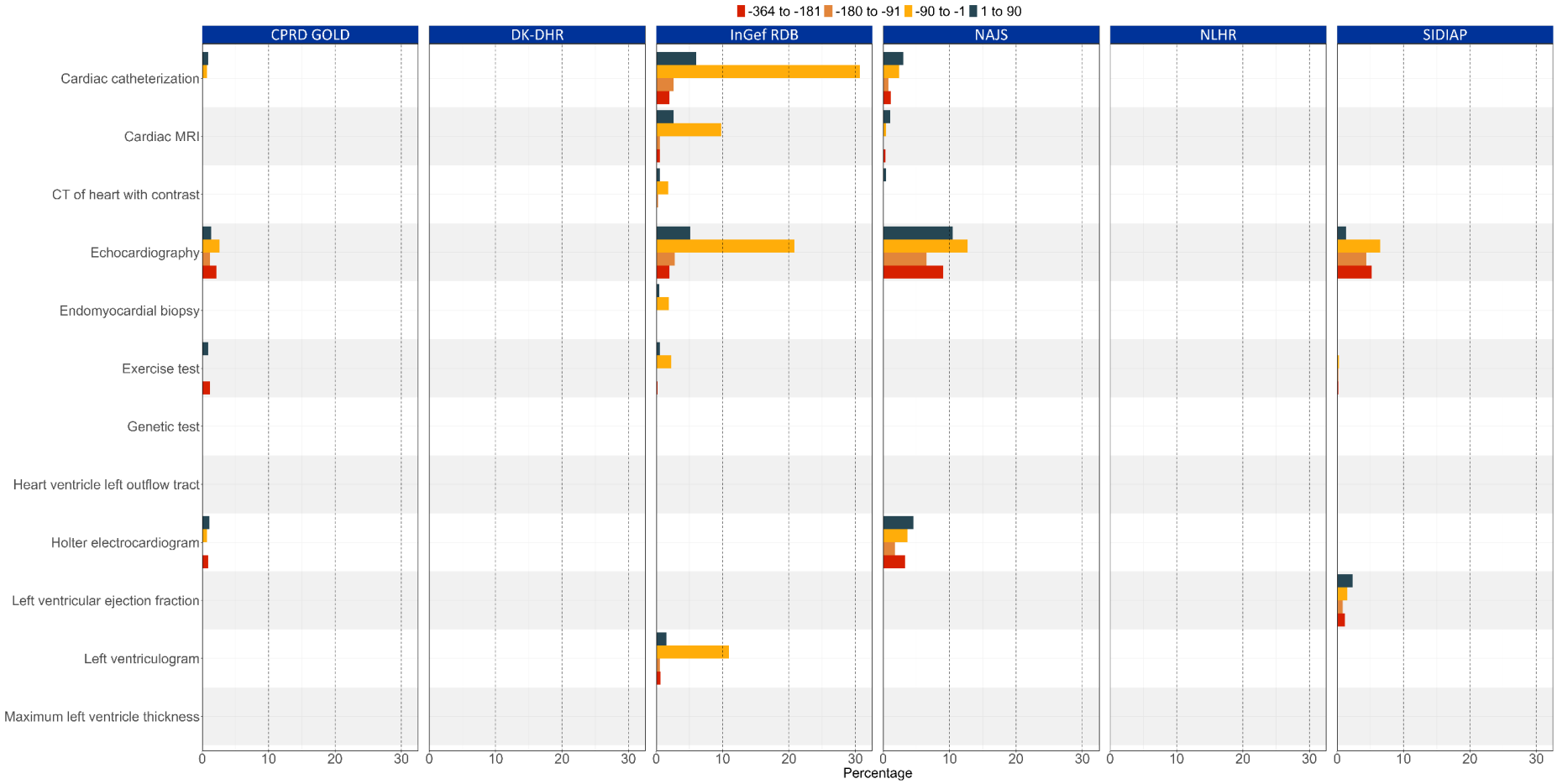
# 17. ANNEXES

Appendix 1: Frequency (%) of selected comorbidities, measurements, medications, and procedures by time windows and study database in females with HCM.

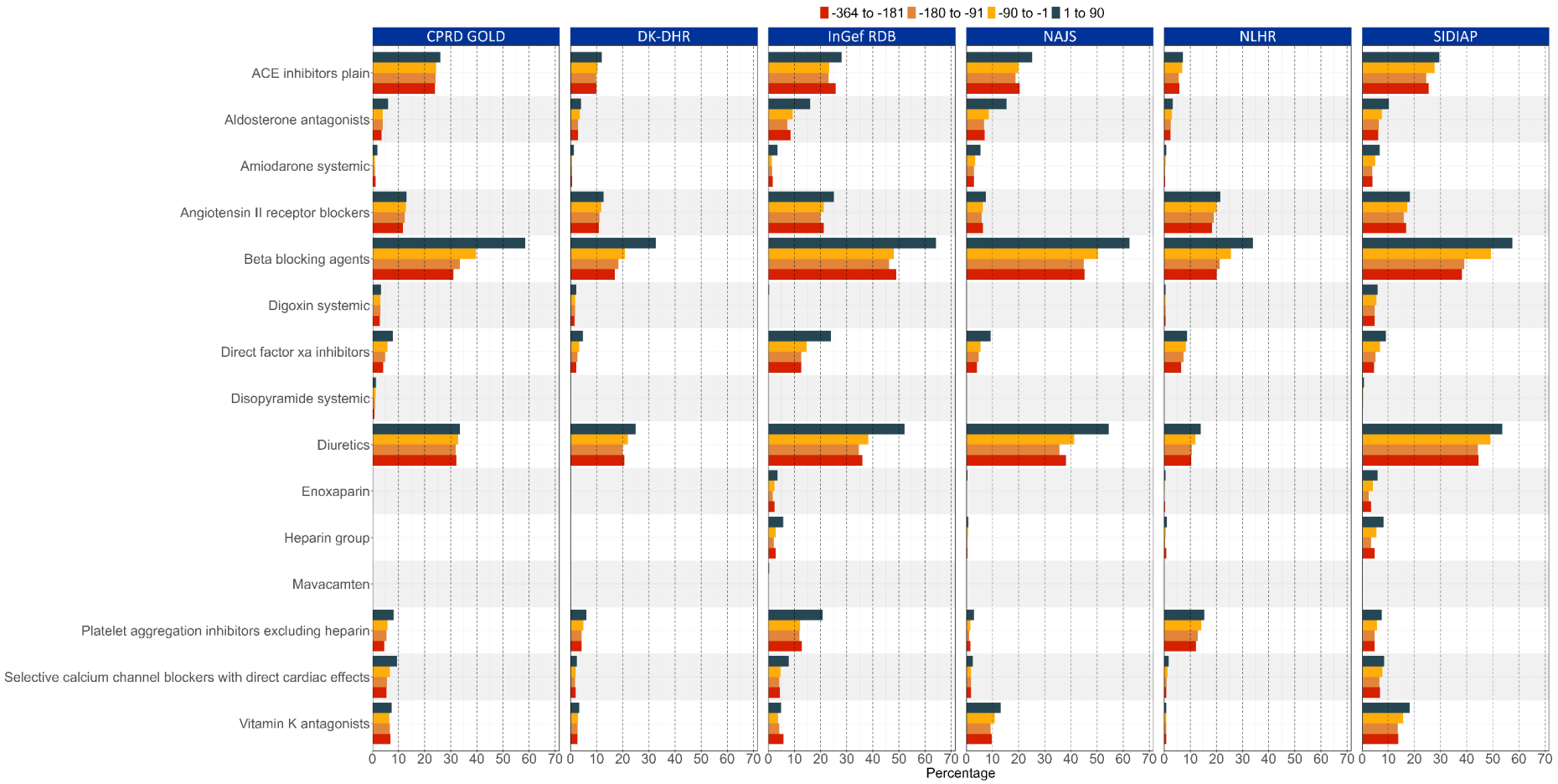
(A) Comorbidities



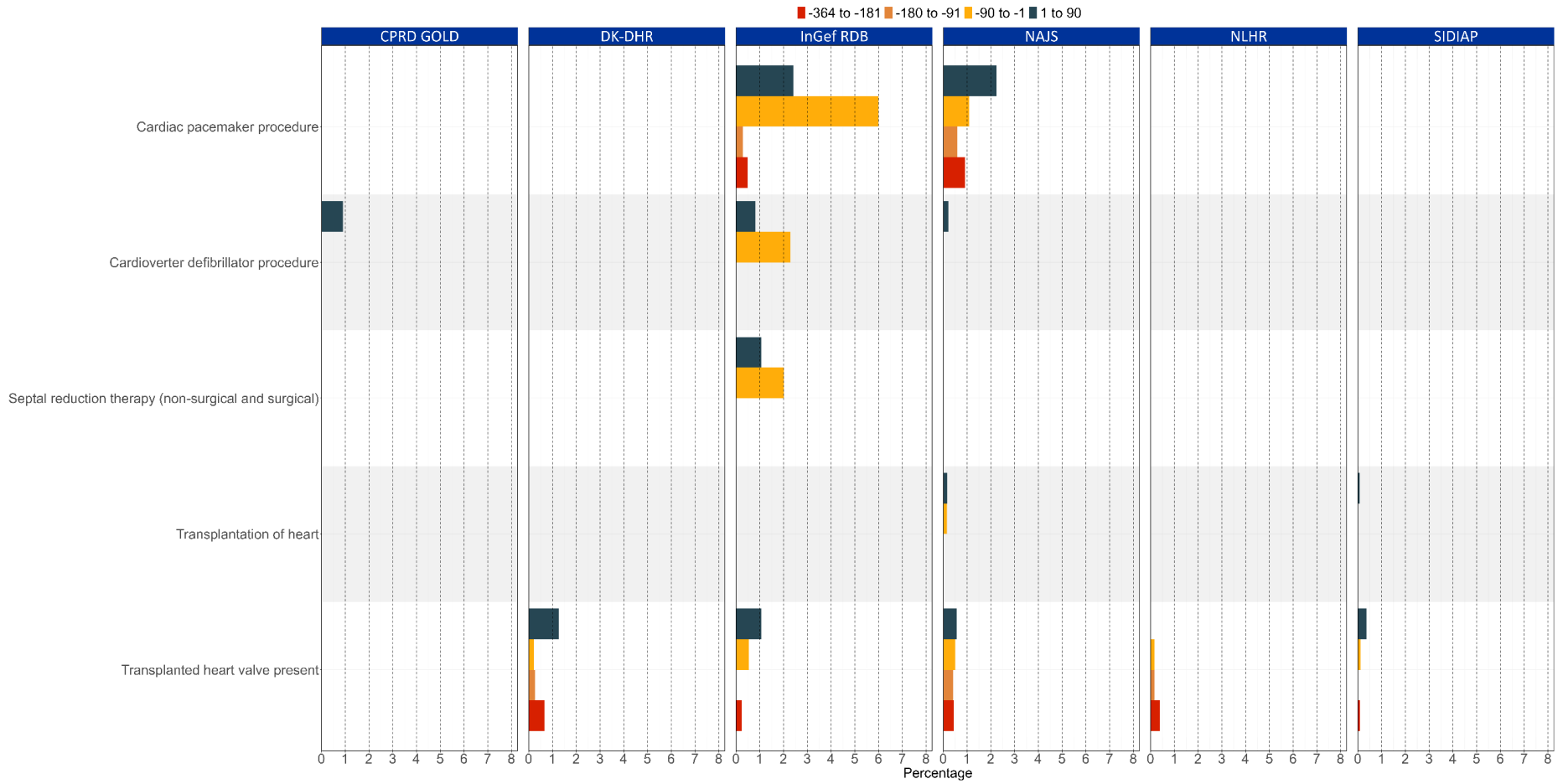

(B) Measurements




(C) Medications

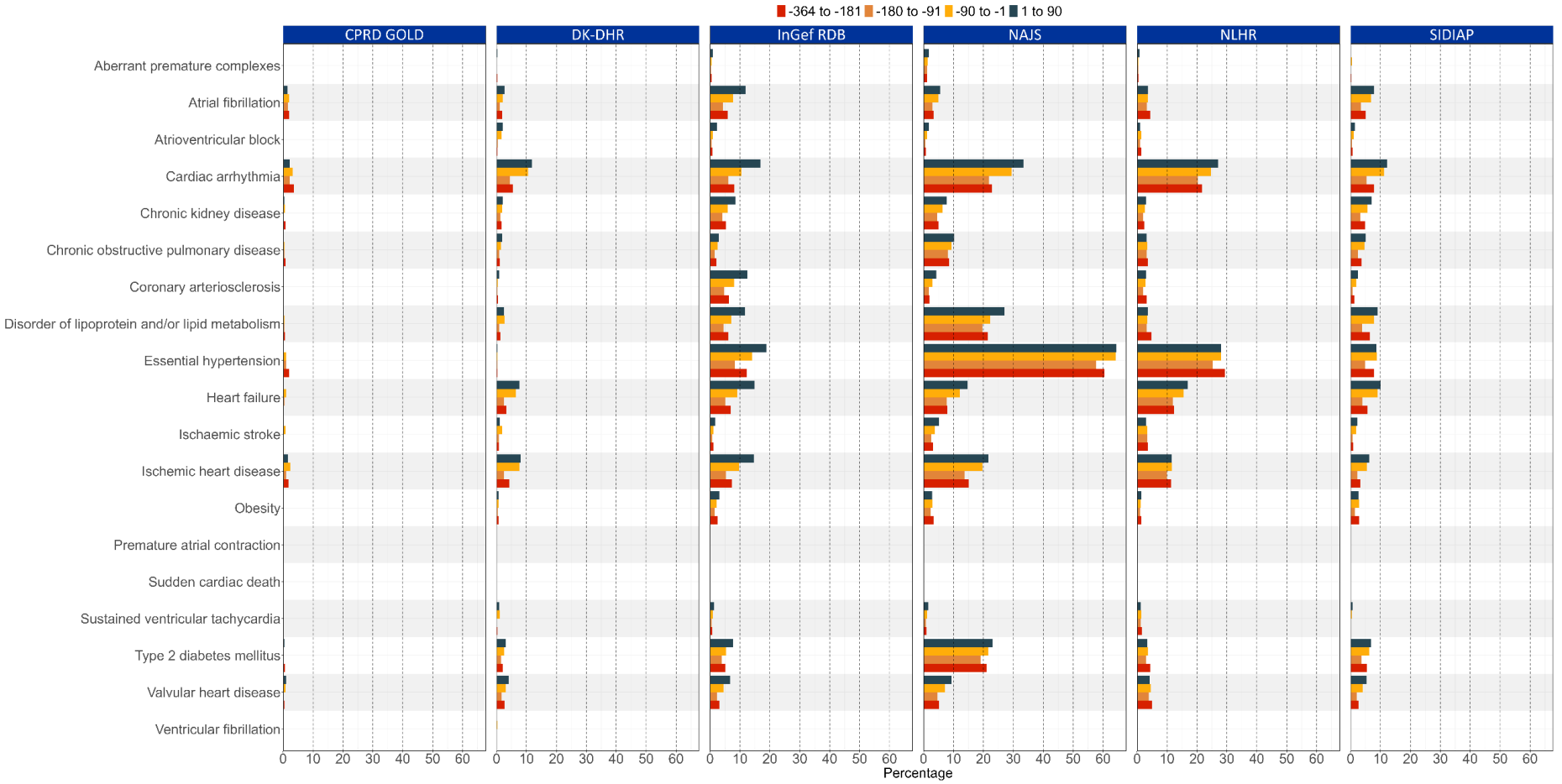



(D) Procedures

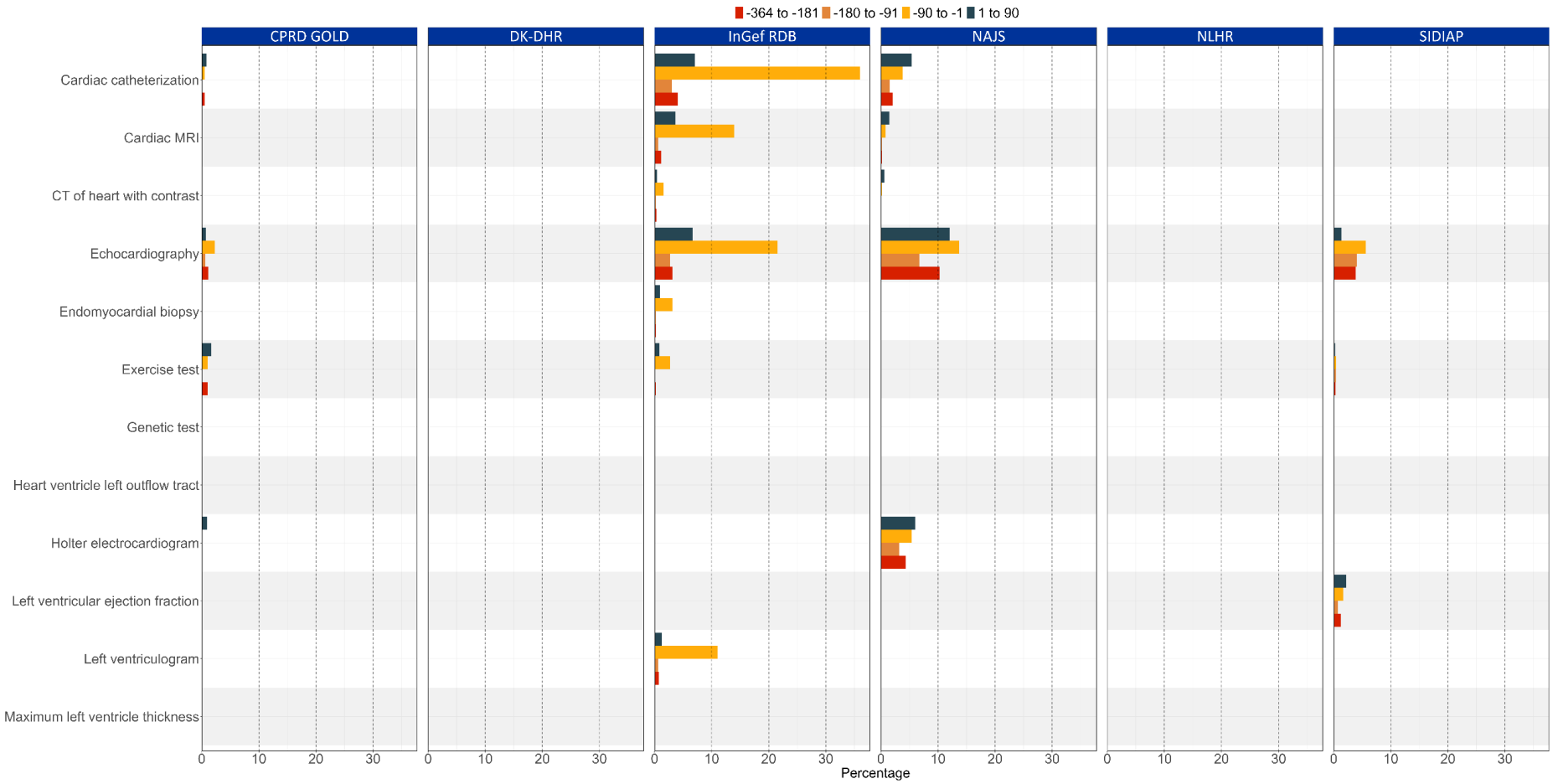



Appendix 2: Frequency (%) of selected comorbidities, measurements, medications, and procedures by time window and study database in males with HCM.

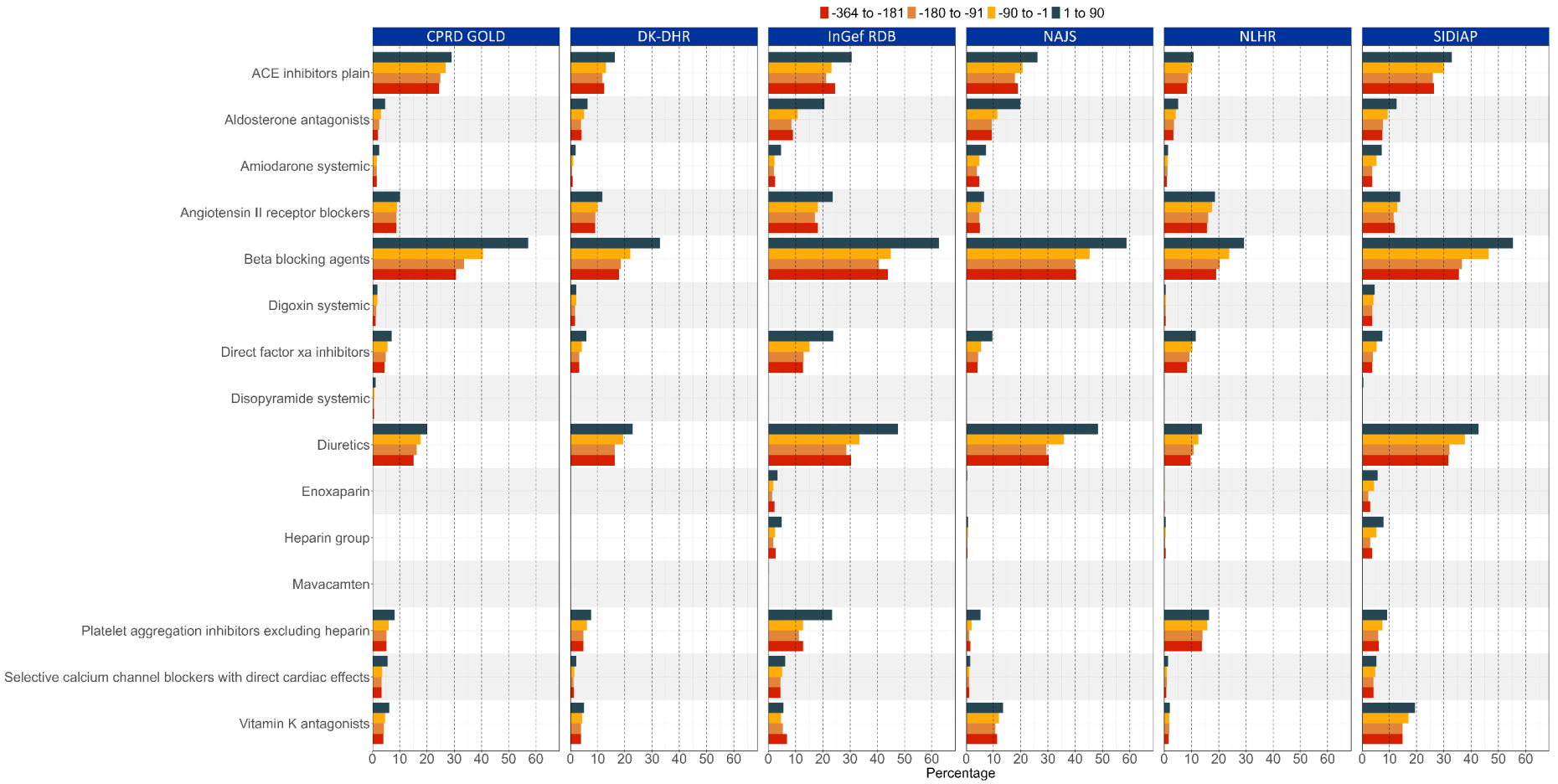
(A) Comorbidities



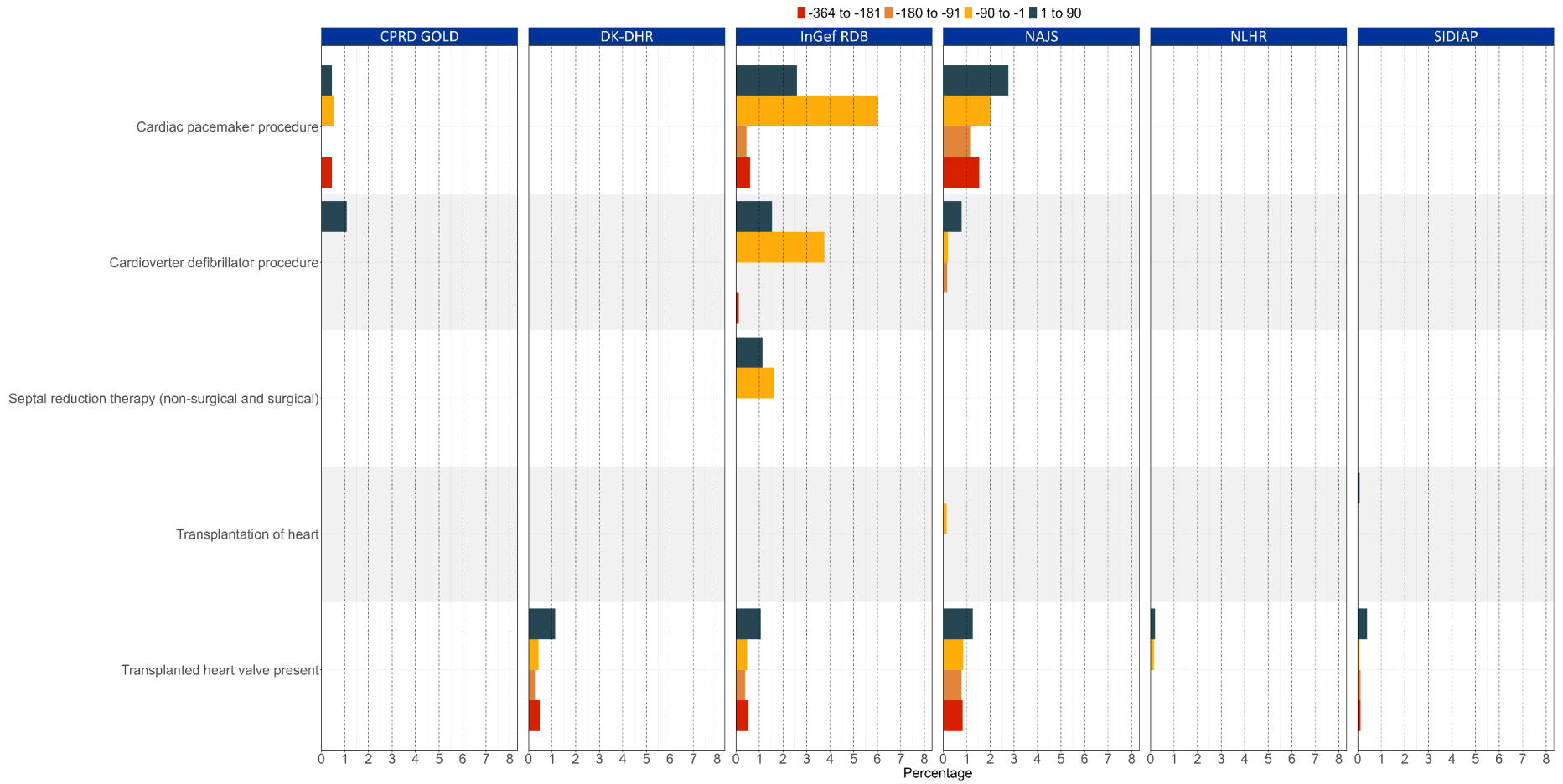

(B) Measurements




(C) Medications

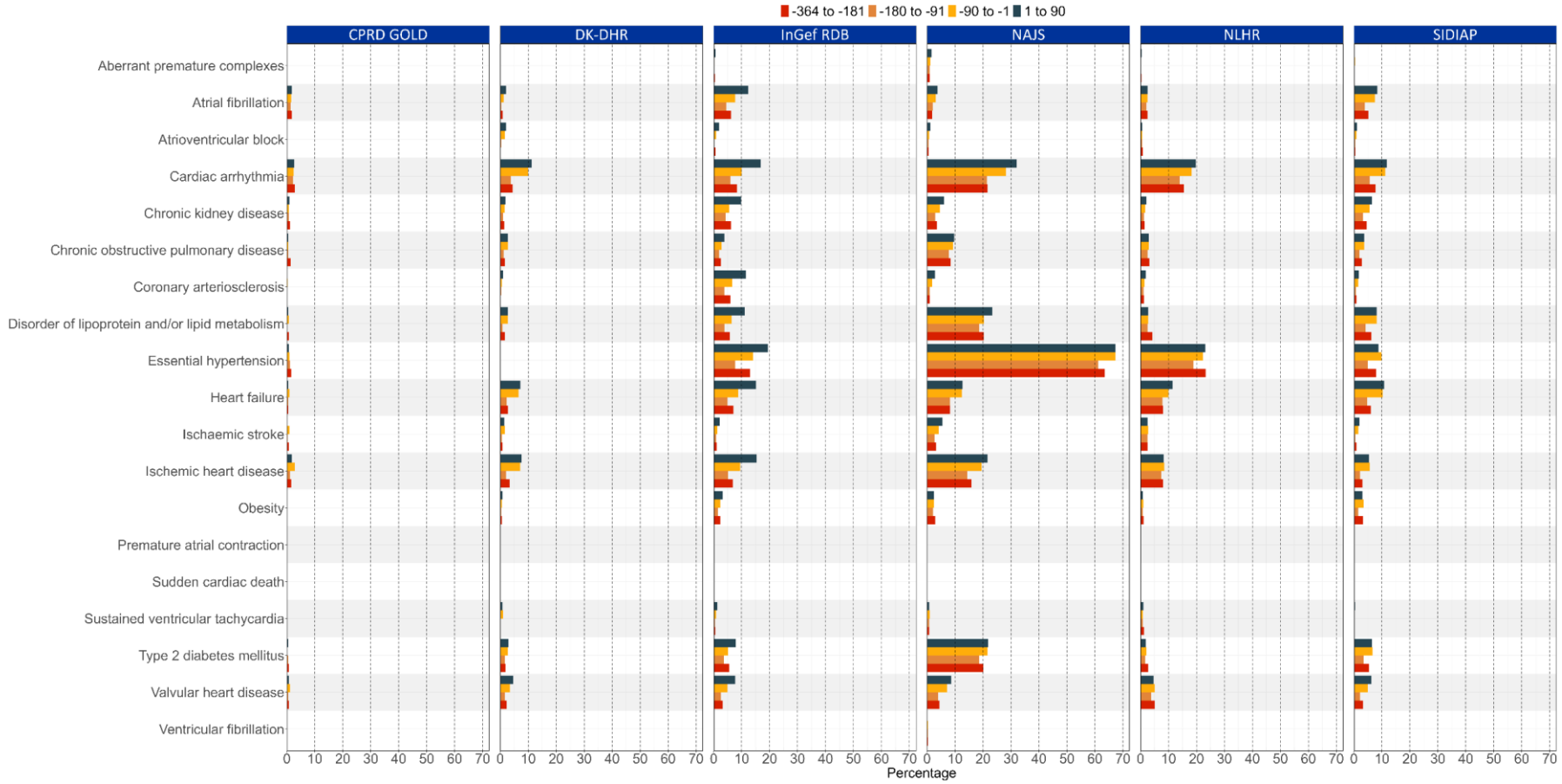



(D) Procedures

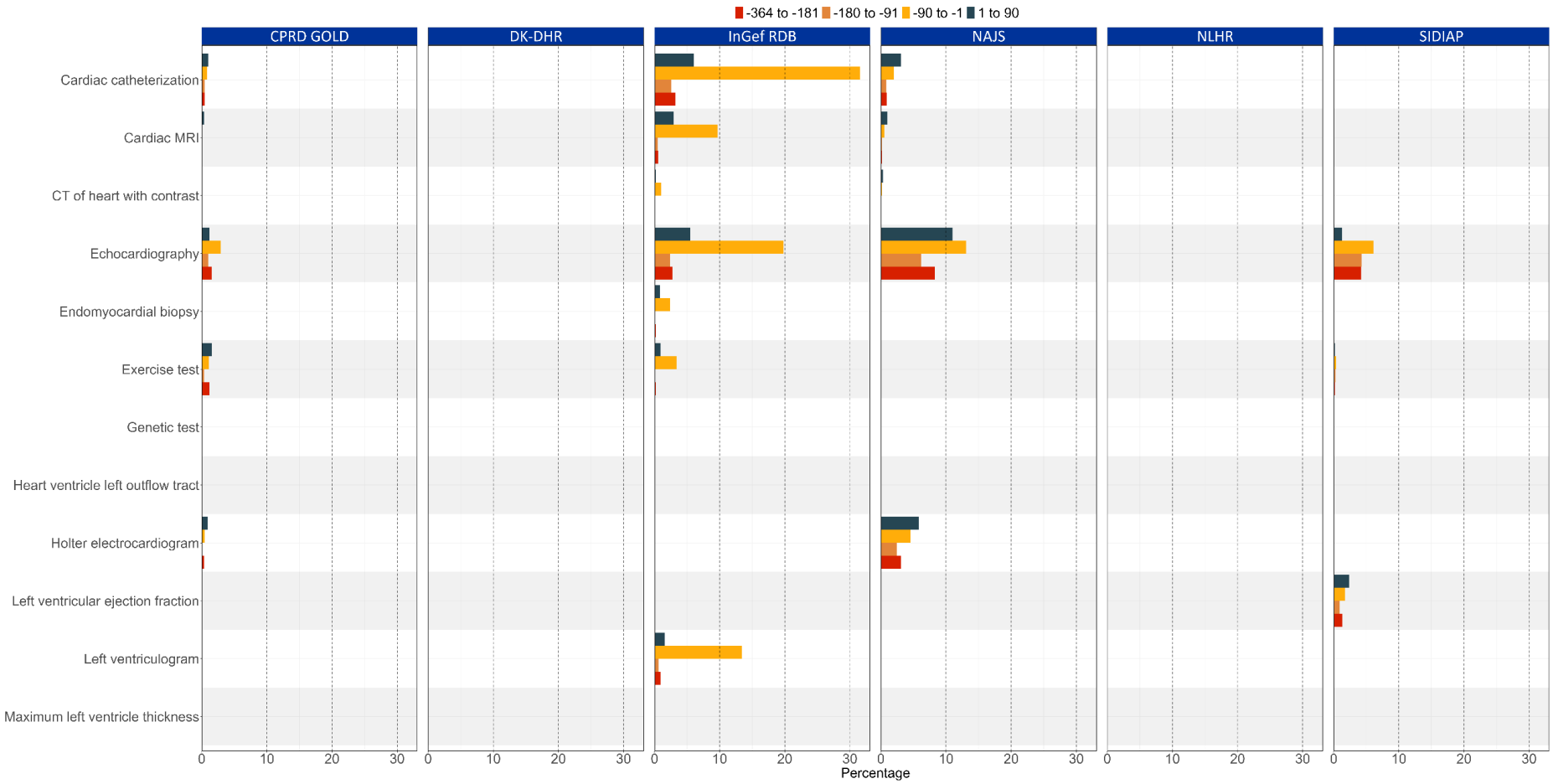



Appendix 3: Frequency (%) of selected comorbidities, measurements, medications, and procedures by time window and study database in individuals with the first recorded HCM diagnosis before 2020.

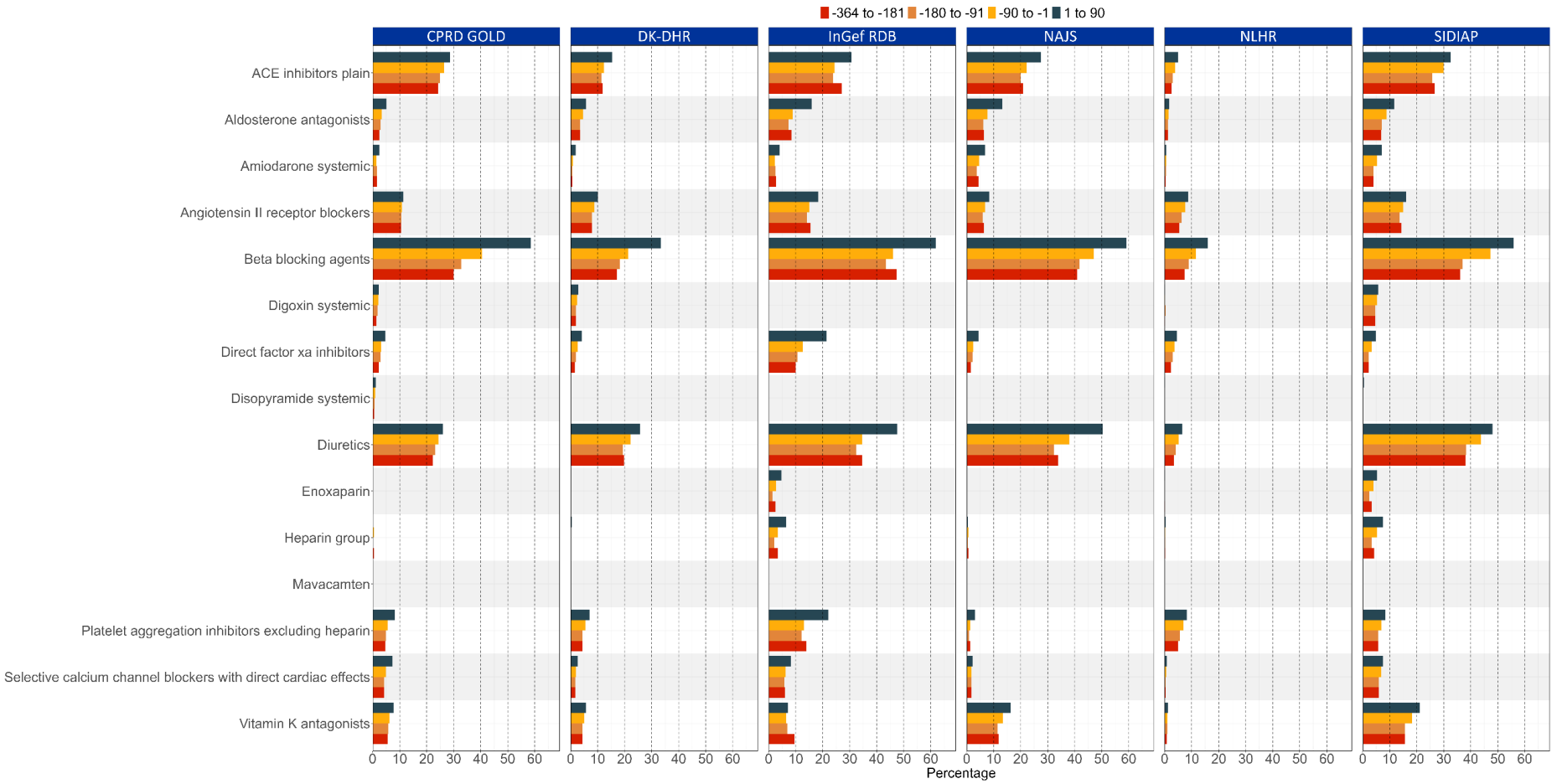
(A) Comorbidities



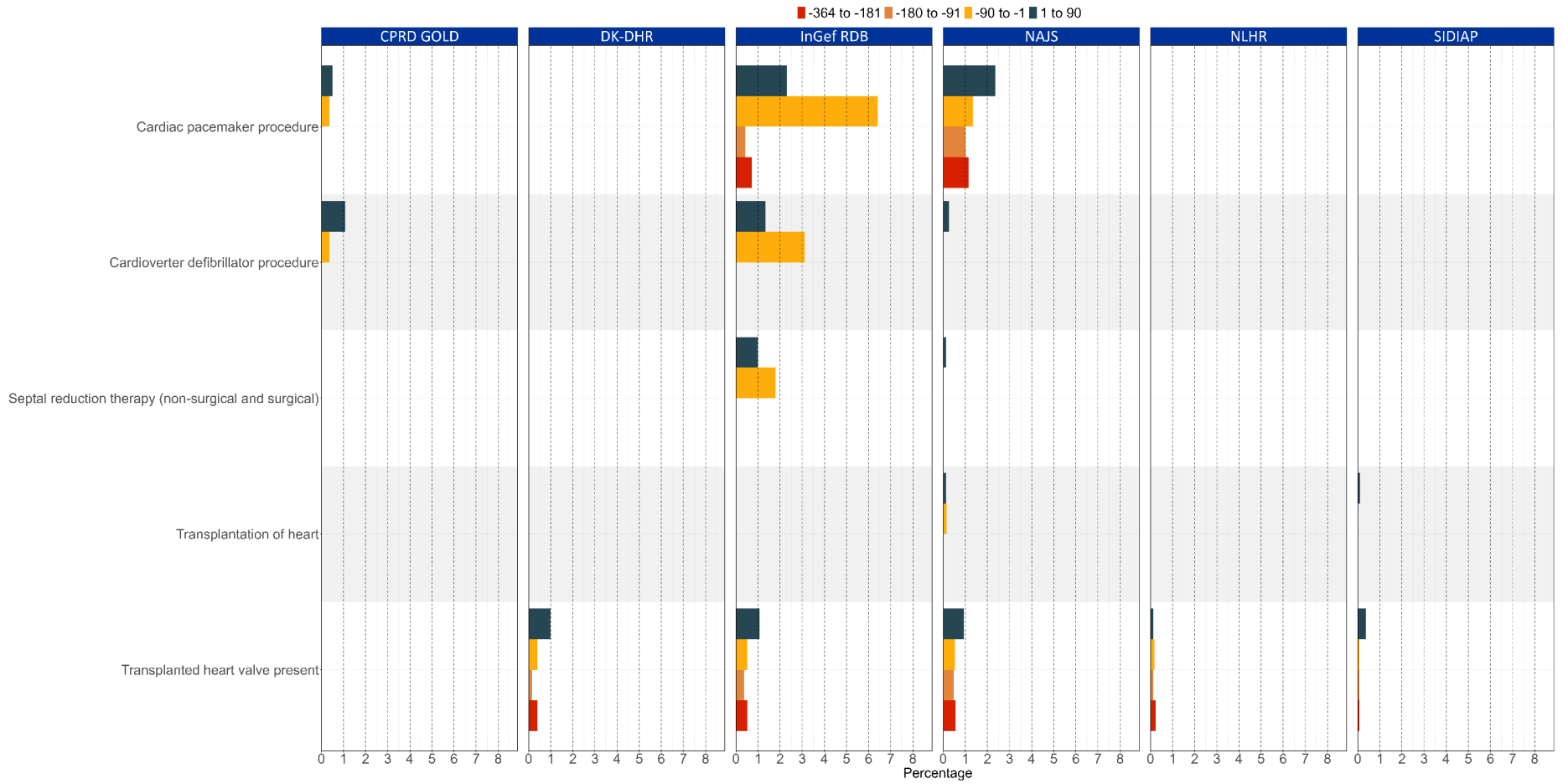

(B) Measurements




(C) Medications

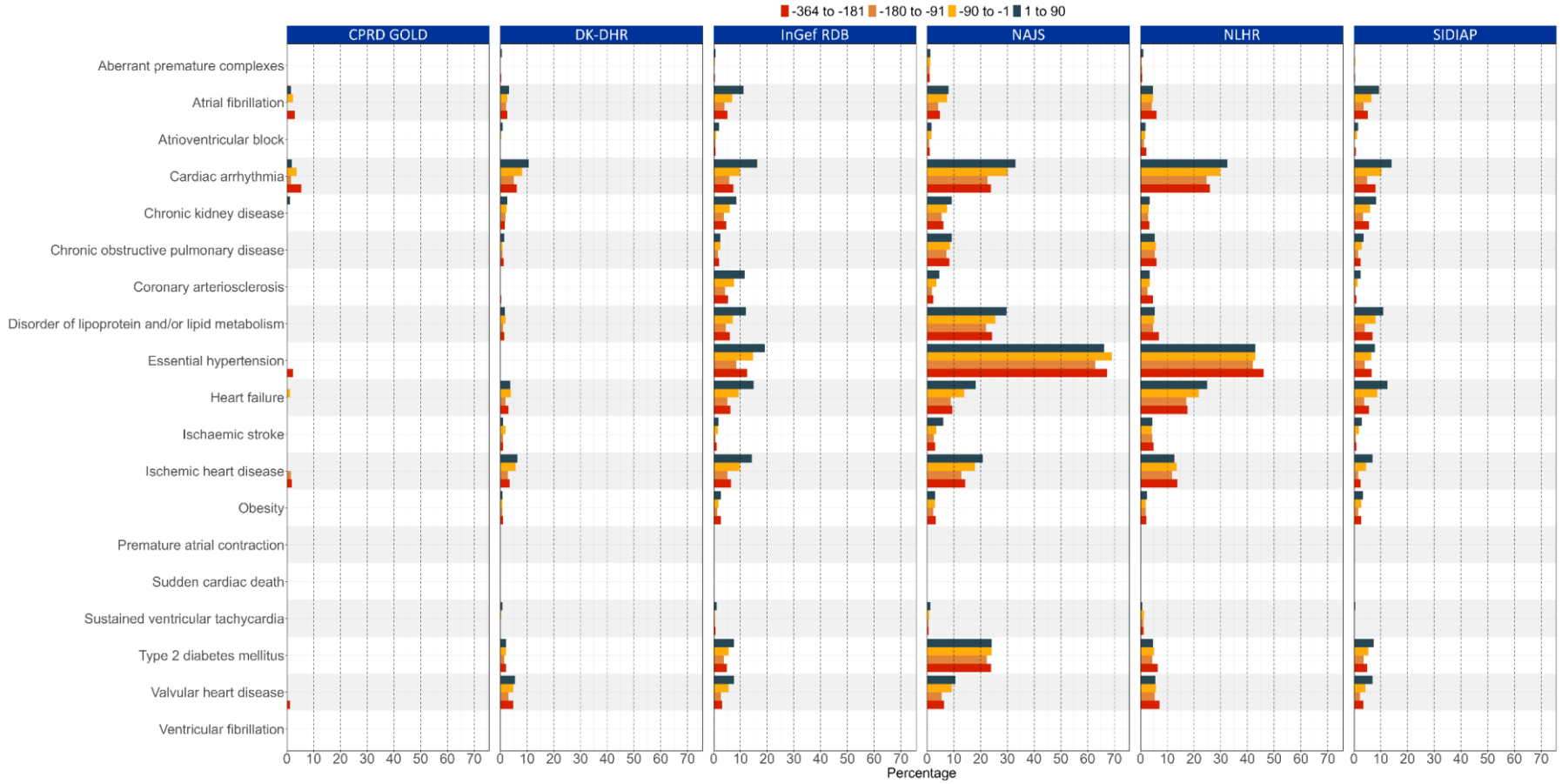



(D) Procedures

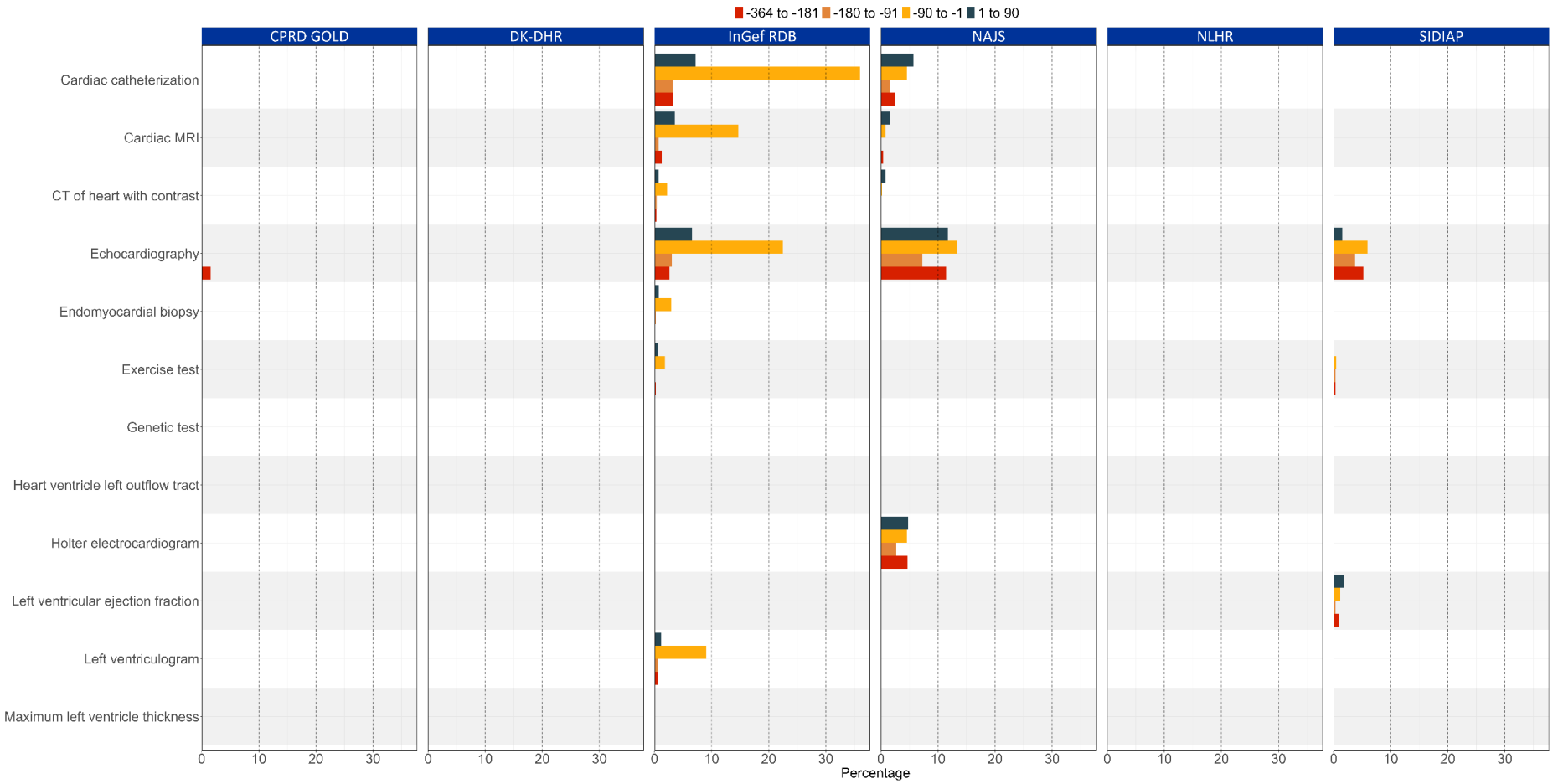



Appendix 4: Frequency (%) of selected comorbidities, measurements, medications, and procedures by time window and study database in individuals with the first recorded HCM diagnosis in or after 2020.

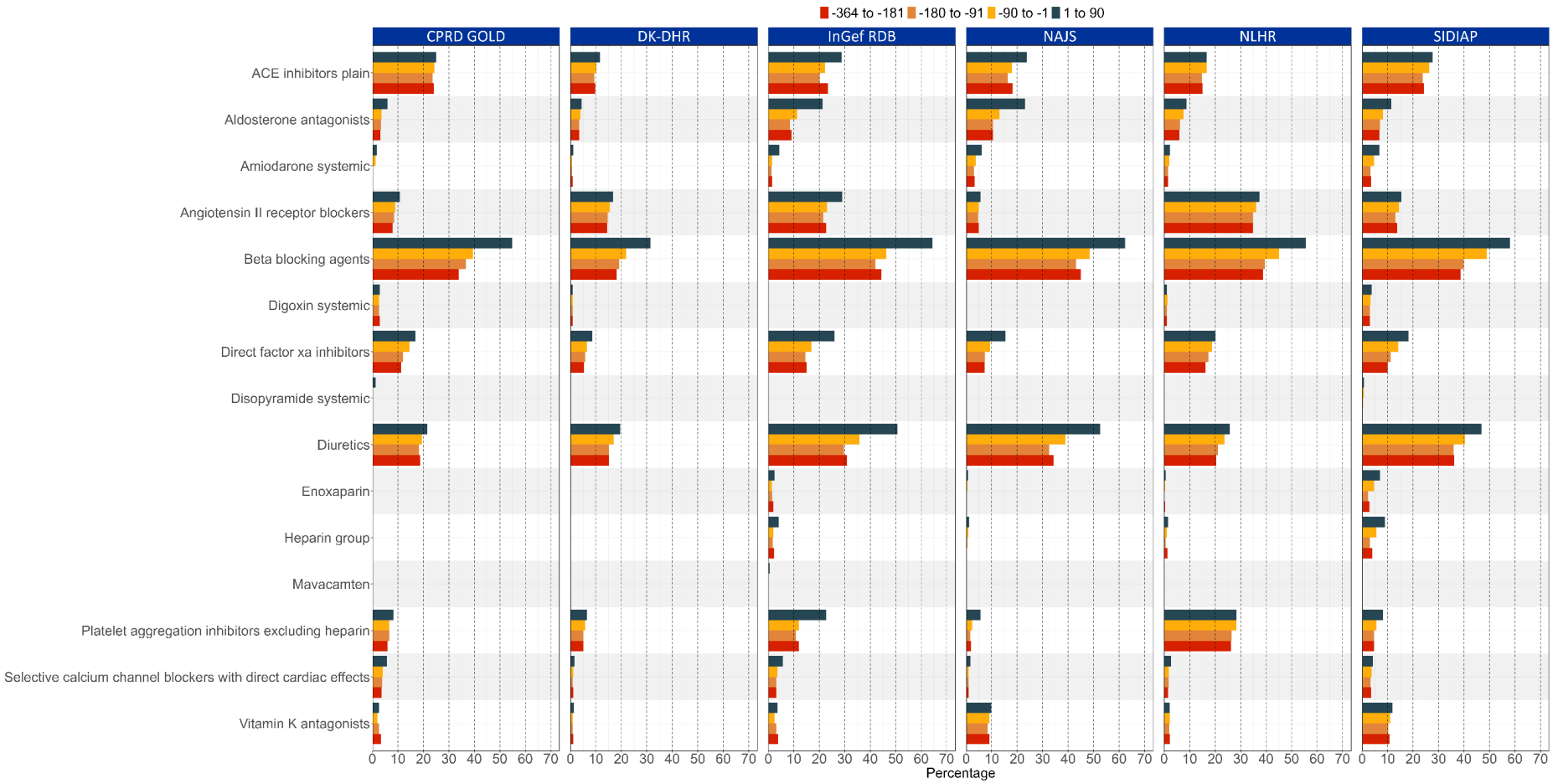
(A) Comorbidities



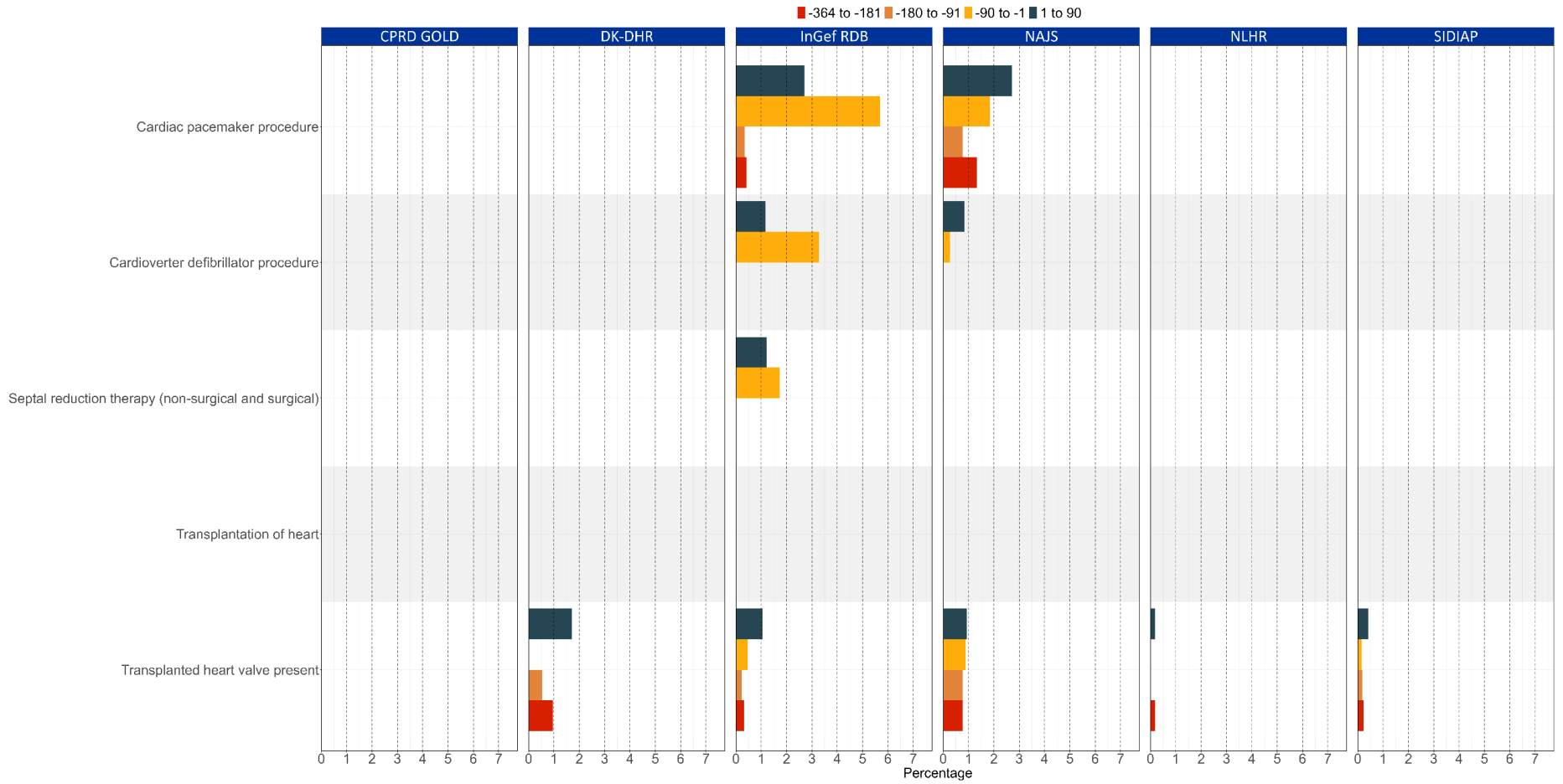

(B) Measurements




(C) Medications

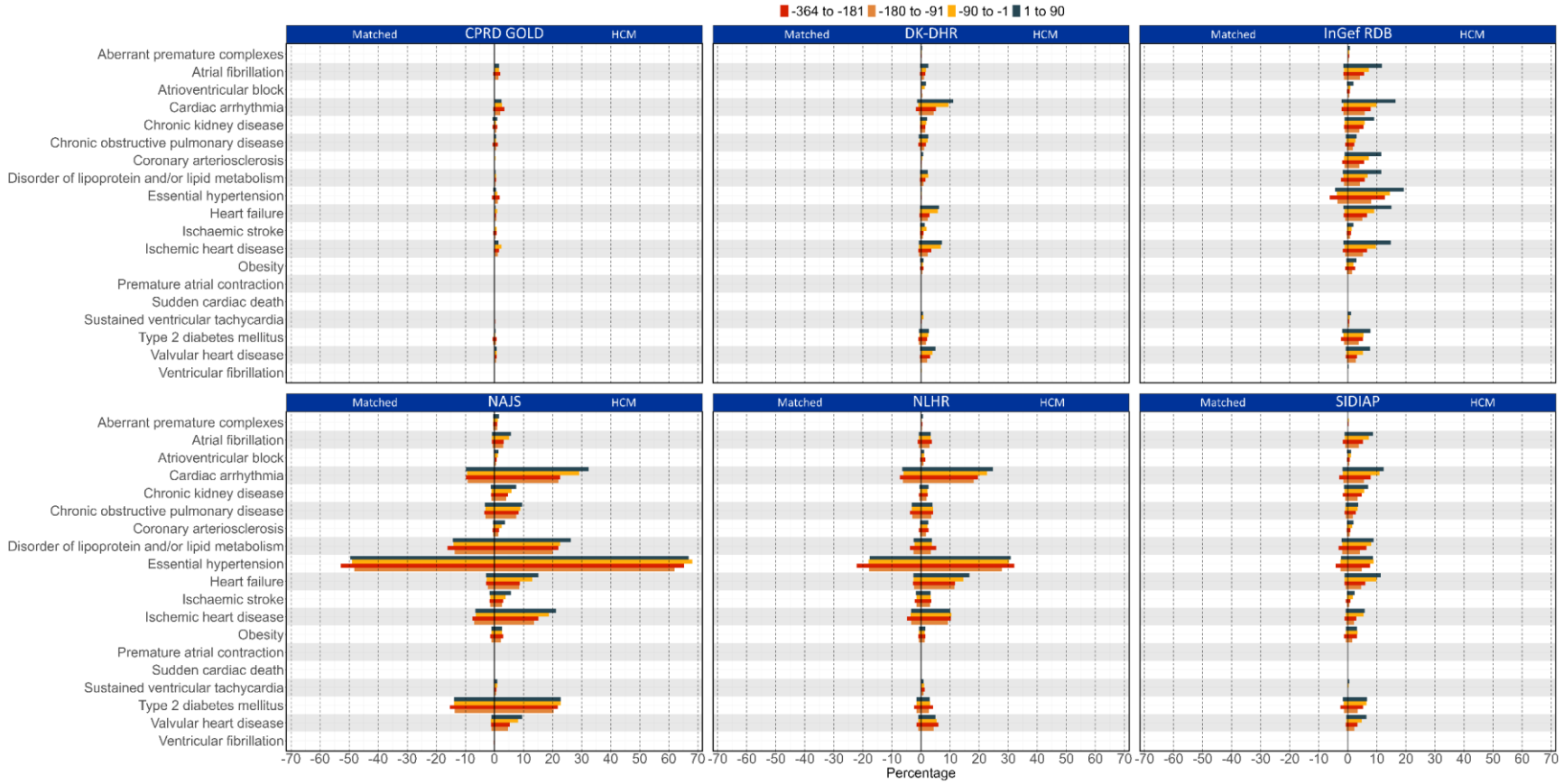



(D) Procedures

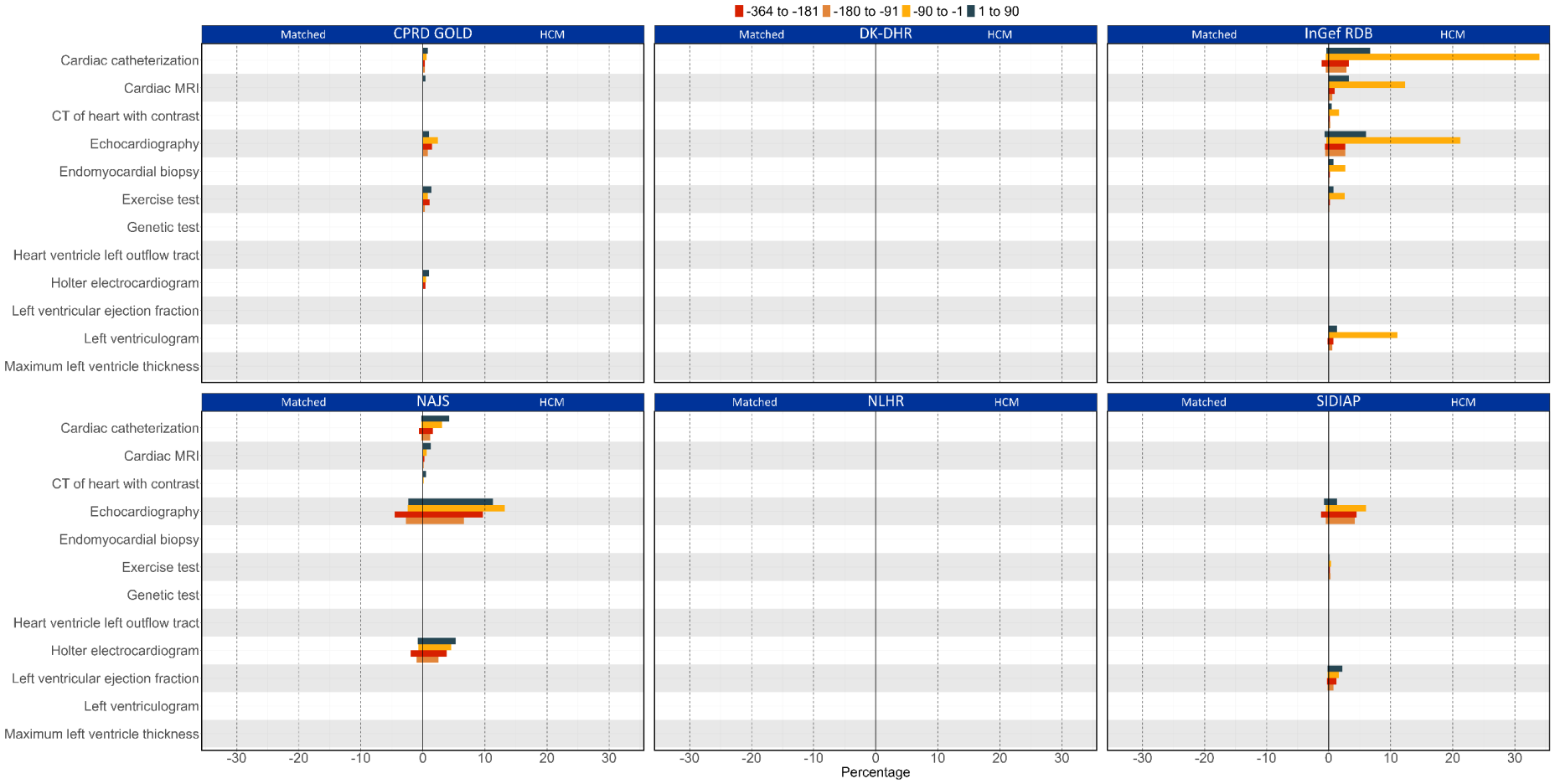



Appendix 5: Comparison of (A) comorbidities, (B) measurements, (C) medications, and (D) procedures in the HCM cohort versus an age- and sex-matched general population sample. % is presented in the horizontal axis. Positive values correspond to the HCM cohort (only those who found a matched pair), whereas negative values correspond to the general population matched cohort.

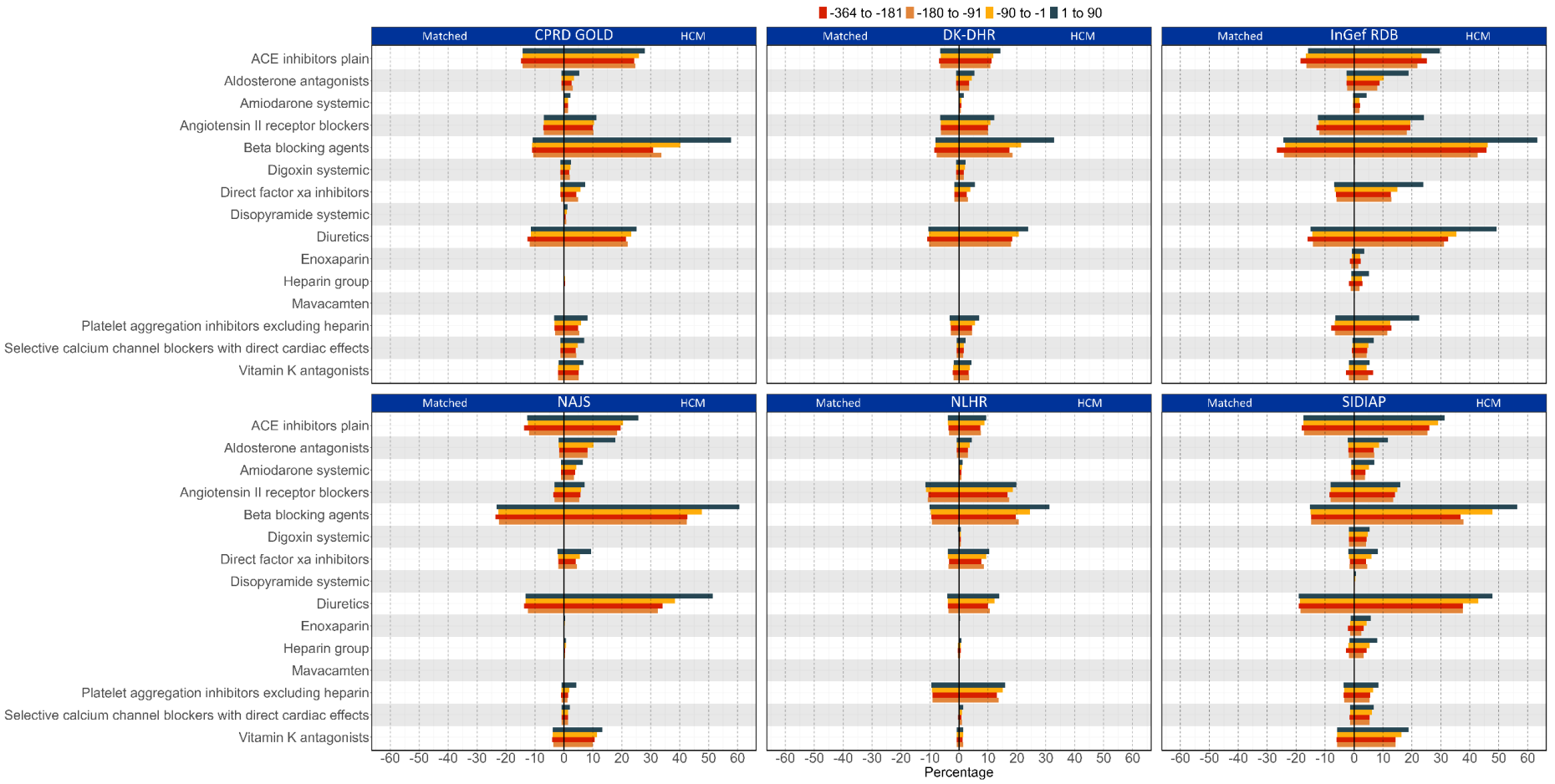
(A) Comorbidities



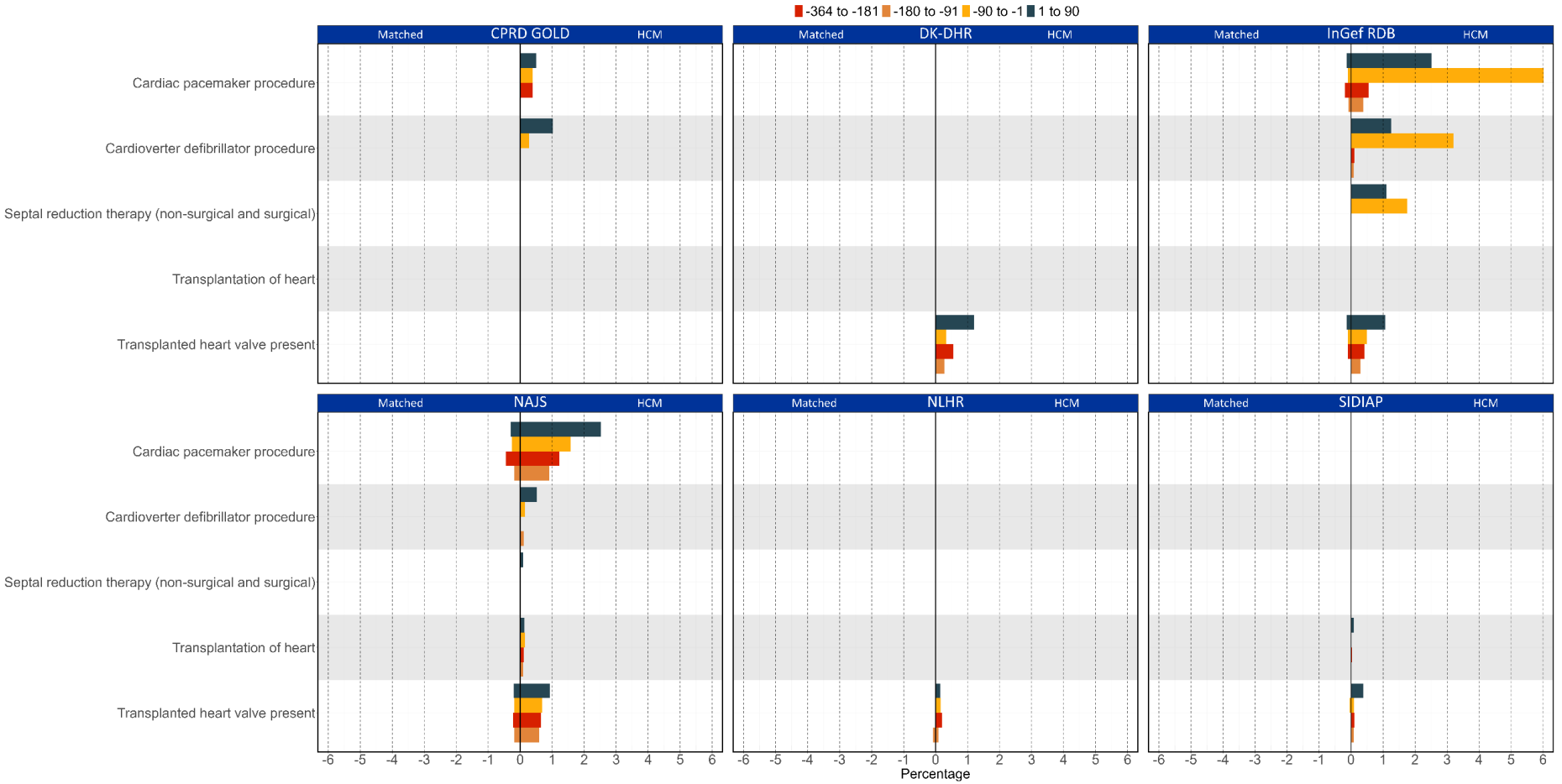

(B) Measurements




(C) Medications




(D) Procedures


-364 to -181
-180 to -91
-90 to -1
1 to 90
Matched
CPRD GOLD
HCM
DK-DHR
InGef RDB
NAJS
NLHR
SIDIAP
Cardiac pacemaker procedure
Cardioverter defibrillator procedure
Septal reduction therapy (non-surgical and surgical)
Transplantation of heart
Transplanted heart valve present
-6 -5 -4 -3 -2 -1 0 1 2 3 4 5 6
Percentage