

BMJ Open Cohort profile: the Coronary Artery disease Risk Determination In Innsbruck by diaGnostic ANgiography (CARDIIGAN) cohort

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ABSTRACT

Purpose The Coronary Artery disease Risk Determination In Innsbruck by diaGnostic ANgiography (CARDIIGAN) cohort is aimed to gain a better understanding of cardiovascular risk factors and their relation to the diagnosis and severity of coronary artery disease, as well as to the long-term prognosis in consecutive (including revascularised) patients referred for elective coronary angiography.

Participants The included patients visited the University Clinic of Cardiology at Innsbruck (Austria), which fulfils a secondary and tertiary hospital function. Inclusion took place in the period between February 2004 and April 2008 and resulted in a total of 8296 patients aged 18–91 years; 65% of them were men.

Findings to date There was one follow-up round on vital status through record linkage for 84% of the cohort (those with residence in Tyrol), resulting in a follow-up duration of over 5.5 to nearly 10.0 years among survivors. The data contain basic patient characteristics, cardiovascular risk factors, laboratory measurements, medications, detailed information on the extent and severity of coronary artery disease, revascularisation history, treatment strategy and mortality specifics. A few studies have already been published.

Future plans Various diagnostic and prognostic studies are planned, also concerning complications, competing risks and cost-effectiveness. Collaboration with other research groups is welcomed.

INTRODUCTION

Cardiovascular diseases are prevalent worldwide, and is the leading cause of death both in men and women in Austria.^{1 2} Particularly for coronary artery disease (CAD), up to now research into the determinants, such as the Framingham Heart Study, has focused mainly on aetiology and prognosis,³ and only few studies pertain to the predictors of diagnosis or severity of angiographically ascertained CAD in larger cohorts.

Originally the cohort was implemented as a screening programme to attain more insights into the set of risk factors and

Strengths and limitations of this study

- This large consecutive Coronary Artery disease Risk Determination In Innsbruck by diaGnostic ANgiography (CARDIIGAN) patient group has good and detailed data, especially on coronary arteries and past interventions; thus, it is possible to address many relevant clinical research questions.
- Several possible sources of selection bias are ruled out through elective ‘all-comer’ recruitment in routine practice.
- There are no data on non-invasive diagnostic results before inclusion in the cohort and no storage of serum and urine.
- This is a single-centre cohort, so external validity can be questionable with certain topics.
- Some data are missing due to limited resources during daily routine.

their relation to and their predictive value to the diagnosis and severity of CAD of consecutive patients referred for elective cardiac catheterisation to the Department of Cardiology at the University Hospital of Innsbruck, Austria. An additional aim was quality inspection on risk factor control and therapeutic strategies. Additionally, the programme enables comparison of the patients in the referral area of our hospital with those of other studies and registries, thereby optimising the risk management of our patients. A few years ago, retrospectively more information on coronary arteries was extracted and survival information from the regional social security registry was linked,⁴ thereby finally establishing the Coronary Artery disease Risk Determination In Innsbruck by diaGnostic ANgiography (CARDIIGAN) cohort. It was then that the potential of this cohort was fully recognised and research questions were further worked out, starting with the diagnostic ones.

COHORT DESCRIPTION

Initial patient inclusion was between February 2004 and April 2008, resulting in a total of 8296 consecutive patients of 18 years and older electively referred for invasive evaluation of a suspected CAD. After informed consent was obtained, they received conventional coronary angiography (CA) by the standard Judkins technique, predominantly via the femoral approach. The participation of a patient did not lead to any excess risks. Blood chemistry was done in the context of daily clinical routine, as was the execution of the study itself.

The cohort was 65% male and on average 63 years of age (between 18 and 91 years). A part of the cohort consists of patients with history of coronary revascularisation (percutaneous coronary intervention or coronary artery bypass grafting). This subgroup with 1897 persons has a higher male proportion of 75% with similar age (average of 64 years, between 28 and 91 years). Another, partly overlapping subgroup of CARDIIGAN has CAD as the leading diagnosis ($n=7081$), at the exclusion of those referred for cardiac catheterisation due to a specific extracardiac condition (eg, solid organ transplantation) or cardiac disease other than CAD (such as heart transplantation or valvular and congenital heart disease). Of these patients with CAD, 5931 (84%) presented for the first time with this diagnosis. Since the University Clinic Innsbruck serves as a secondary as well as a tertiary hospital, a portion of the cohort members came from outside the primary catchment area (thereof nearly a quarter from abroad) of the regional social security service of Tyrol. This regional system is the source of the data on vital status. Thus these data are available for about 84% of the patients, the so-called 'local' patient group (figure 1). Many of the other 16% of patients are typical of the tourism in this region and would probably often be incomparable with patients of cardiology clinics elsewhere.

Most data entry was done shortly after the patient was presented to the clinic. A part of the information (detailed laboratory data) was extracted from patients' charts after discharge and another part (final CA report) retrospectively, when the large potential of the cohort was realised and more details on the arteries deemed invaluable for relevant research questions. Also, a first record linkage was performed to assess survival status, with the date and cause of death, of the 'local' part of the CARDIIGAN cohort. Thereby there is information on survival of the highest possible quality,^{5,6} available up to 1 January 2014, resulting in over 5 years of follow-up per person. During the first 5 years 13% had died. More linkage is now planned to update information on survival status, but also to assess the status of other events. Particularly data on various cardiovascular disease outcomes are to be gathered to enable appraisal of subsequent manifestations of arterial diseases.

Since the data documentation had to fit into the daily routine with limited time resources, some entries were incomplete and thereby a part of the data are missing.

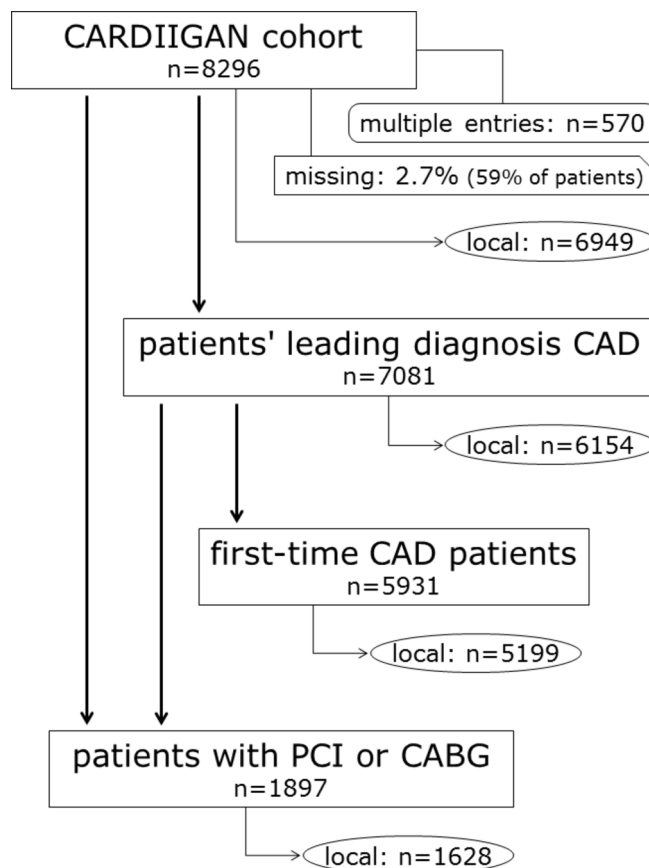


Figure 1 Subgroups of the CARDIIGAN cohort. The term 'local' indicates that survival data are available from the regional social security system. CABG, coronary artery bypass grafting; CAD, coronary artery disease; CARDIIGAN, Coronary Artery disease Risk Determination In Innsbruck by diaGnostic ANgiography; PCI, percutaneous coronary intervention.

Of the clinical data 2.7% were lost, which concerns some 59% of the 8296 patients. As for the medication information, the documentation occurred suboptimally and so 47% was missing. The problem of missing values will be handled by applying multiple imputation techniques.^{7,8}

Table 1 shows the characteristics of the included patients, and basic data include residence, sex, age, height, weight and smoking status. Also symptoms of angina pectoris according to the so-called Canadian Cardiovascular Society score,⁹ hypertension (<140/90 mm Hg or relevant medication¹⁰), diabetes mellitus (fasting plasma glucose ≥ 126 mg/dL or medication¹¹) and family history of premature myocardial infarction (first degree: male relative at age <55 years, female relative at age <65 years¹²) have been documented, as well as seven types of medication (antianginal, antihypertensive and lipid-lowering). On the laboratory parameters, there are 15 different parameters, including lipids. Detailed information on the three major coronary arteries and their main side branches, including the extent and severity of atherosclerotic obstructions and prior or current interventions, is available. Stenoses of the arteries were categorised into 0%, less

Table 1 Characteristics of the cohort participants in CARDIIGAN (n=8296)

Characteristics	Specifics	Missing (n)
Sex	Female: 2908 (35%) Male: 5388 (65%)	0
Age at baseline (years), mean (SD)	63 (11)	0
Residence	Tyrol: 6949 (84%) Rest of Austria: 1027 (12%) Foreign: 320 (4%)	0
Height (m), mean (SD)	1.71 (0.09)	117
Weight (kg), mean (SD)	78.4 (14.9)	118
Smoking status	Never: 3660 (52%) Former: 1929 (27%) Current: 1495 (21%)	1212
Angina pectoris complaints	None: 3671 (44%) Stable: 2986 (36%) Unstable: 1269 (15%) Atypical: 370 (4%)	0
Myocardial infarction	None: 6523 (79%) STEMI: 459 (6%) NSTEMI: 631 (8%) MCI: 683 (8%)	0
Valvular/congenital heart disease	No: 6395 (87%) Yes: 957 (13%)	944
Cardiomyopathy	No: 3793 (86%) Yes: 594 (14%)	3909
Solid organ transplantation	No: 8128 (98%) Yes: 168 (2%)	0
Hypertension	No: 2227 (27%) Yes: 6069 (73%)	0
Diabetes mellitus	No: 6902 (83%) Yes: 1394 (17%)	0
Family history of myocardial infarction (first-degree relative: male <55 years; female <65 years)	No: 6532 (79%) Yes: 1764 (21%)	0
Lipid-lowering medication: statin	No: 2521 (46%) Yes: 2967 (54%)	2808
Antihypertension/anti-anginal medication	No: 1141 (20%) Yes: 4434 (80%)	2721
Total cholesterol (mg/dL), mean (SD)	193 (45)	585
HDL cholesterol (mg/dL), mean (SD)	54.9 (17.0)	741
LDL cholesterol (mg/dL), mean (SD)	123 (38)	756
Triglycerides (mg/dL), median (IQR)	126 (91–175)	591
Fibrinogen (mg/dL), median (IQR)	367 (297–459)	265
C reactive protein (mg/dL), median (IQR)	0.28 (0.12–0.70)	207
Prothrombin time (%), mean (SD)	103 (13)	151

Continued

Table 1 Continued

Characteristics	Specifics	Missing (n)
Thrombocytes ($\times 1000$ U/ μ L), mean (SD)	233 (67)	147
Haemoglobin (g/dL), mean (SD)	14.3 (2.3)	119
Creatinine (mg/dL), mean (SD)	1.07 (0.72)	105
Gamma-glutamyltransferase (U/L), median (IQR)	33 (21–54)	321
Uric acid (mg/dL), mean (SD)	6.33 (1.76)	970
Urea (mg/dL), median (IQR)	35.4 (29.1–44.4)	248
Maximum degree of stenosis	None: 2029 (25%) <50%: 1588 (20%) $\geq 50\%$ –70%: 296 (4%) $\geq 70\%$: 4157 (52%)	226
Number of stents	None: 5918 (76%) 1: 1398 (18%) ≥ 2 : 424 (5%)	556
Number of bypass	None: 7330 (94%) ≥ 1 : 439 (6%)	527
Cause of death (up until 31 December 2013) with complete ICD-10 code	Alive: 5366 (77%) Cardiovascular death: 746 (11%) Other causes: 837 (12%)	1347

CARDIIGAN, Coronary Artery disease Risk Determination In Innsbruck by diaGnostic ANgiography; HDL, high-density lipoprotein; ICD-10, International Classification of Diseases, tenth revision; LDL, low-density lipoprotein; MCI, myocardial infarction; NSDSTEMI, non-ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction.

than 50%, 50%–70% and over 70% obstruction. This enables categorisation of CAD into none, non-obstructive, and one-vessel, two-vessel or three-vessel disease. Other outcome measures are proposed treatment and survival status as of 31 December 2013, with date and cause of death.

Patient and public involvement

Patients were not involved in the development and design of the project.

Findings to date

In a first publication, even before the end of the inclusion period, the results on the association of high-density lipoprotein (HDL) cholesterol and C reactive protein in relation to angiographically evaluated CAD were presented and showed that the two biomarkers seem to have an important independent association with the prevalence of the disease (table 2).¹³ More recently, a small study was done focusing on sex differences concerning CAD and cardiovascular risk factors: especially the impact of smoking and hypercholesterolaemia seems to differ between men and women.¹⁴

After completion of patient recruitment and data management processes (including survival data linkage),

Table 2 Extract of the multivariable results from Alber *et al*¹³

All patients	CAD vs non-CAD		Wald statistic
	OR	95% CI	
Age (per year)	1.058	1.051 to 1.066	247.7
Male gender	2.753	2.371 to 3.197	175.9
HDL cholesterol (per mg/dL)	0.976	0.971 to 0.982	77.3
Prior statin use	1.751	1.511 to 2.029	55.3
Smokers	1.720	1.396 to 2.118	25.9
Hypertension	1.494	1.244 to 1.793	18.5
Diabetes	1.539	1.250 to 1.894	16.5
C reactive protein (per log unit)	1.343	1.158 to 1.558	15.1
Total cholesterol (per mg/dL)	1.003	1.001 to 1.005	9.2
Triglycerides (per log unit)	0.917	0.621 to 1.355	0.2

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CAD, coronary artery disease; HDL, high-density lipoprotein.

the focus was on diagnostic prediction modelling. An interim study was presented at a meeting of the Austrian Society of Cardiology¹⁵ and recently a full manuscript was published¹⁶: validation of an existing CAD diagnosis model showed moderate performance, but extension with HDL and LDL cholesterol, fibrinogen and C reactive protein led to a relevant extra net benefit. After this study a more refined polytomous regression analysis was done to predict five ordinal categories of CAD diagnosis, thus enabling a better treatment decision and possibly making some future angiographies unnecessary (accepted publication in *Int J Cardiol* 2018 doi:10.1016/j.ijcard.2018.05.092).^{17 18} Currently we are analysing data on chronic kidney disease to assess the associations of this disease, severity of CAD and mortality as inspired by the work of Brand *et al*¹⁹ and our own previous work.²⁰ Other ideas involve complications,²¹ in particular bleedings,²² competing risks in mortality^{23–26} and cost-effectiveness,^{27 28} especially in the context of prioritisation of vascularisation.^{29 30}

Strengths and limitations

It is unfortunate that survival assessment is not possible for the complete cohort; it is restricted to 84% of the participants. Actually it only involves those people who are residents of Tyrol, so the results apply to a clearly defined group and generalisability is probably not compromised in this respect. Another weakness is the absence of a personal follow-up of patients due to limited available resources at discharge. However, a very good alternative is the feasible and proven record linkage option. It is also unfortunate that there is a lack of information

on non-invasive diagnostic modalities and results, since these might be relevant in the diagnostic work-up. This, and other aspects of the healthcare system, might lead to some selective referral bias, and one must be careful when interpreting the results. On the other hand, possible selection is counteracted because of the patients being assigned to a wide range of doctors, that is, general practitioners, internists and cardiologists. Ideally, research possibilities would have been enhanced if serum and urine could have been stored at the time to enable future additional laboratory tests, making it possible to include various novel biomarkers currently being introduced in this field.³¹ Furthermore, we are inevitably confronted with missing information since the daily routine did not always allow complete registration of data; however, there are statistical imputation techniques to compensate for this limitation.

As for the strengths, this consecutive patient group comprises a large clinical cohort with 5–10 years of follow-up, with good and detailed data. The study involves an elective ‘all-comer’ recruitment, which excludes some potential sources of selection bias. Also, the study represents routine practice and therefore allows the assessment of the effectiveness of certain procedures, as opposed to the ideal case scenarios. Particularly valuable are the data on various routine laboratory results and extensive information on the arteries and past interventions.

COLLABORATION

Cooperation with other researchers is very much favoured. A contact has already been established with a local neurological research group. Furthermore, international participation is being searched for with experts in various fields. Particularly Ewout Steyerberg, professor of clinical biostatistics and medical decision making and one of the leading scientists in clinical prediction models,³² has been welcomed to theoretically strengthen our research group. Also, Ben van Calster has been involved for his expertise on multinomial risk models.³³ Collaboration with other research groups with comparable data to enable external validation studies would be beneficial to further the prediction modelling plans. For more information the corresponding author (ME) can be contacted (Michael.Edlinger@i-med.ac.at).

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Contributors HFA, JD and MW initiated the project and coordinated the data entry. MW extracted extra detailed data on the coronary arteries. ME was responsible for data management and preparation. MW wrote the manuscript. HFA is the PI of the CARDIIGAN cohort. HFA, JD and ME revised the manuscript critically. All authors are accountable for this work.

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Competing interests None declared.

Patient consent Obtained.

Ethics approval Approval was obtained, for both the original study group and the extension to a cohort with ascertained survival status, from the ethical committee of the Medical University of Innsbruck (UN3266 and AN3266).

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement Collaboration is welcomed and data sharing can be agreed upon. The corresponding author can be contacted.

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