Declining risk of ischemic heart disease over time in rheumatoid arthritis: 1821 patients from 1972 to 2017.

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Abstract

Objectives: To evaluate trends of acute myocardial infarction (AMI) and ischemic heart disease (IHD) in rheumatoid arthritis (RA) patients compared with the general population over time.

Methods: We performed a retrospective cohort study of 1821 RA patients diagnosed from 1972 to 2013. The total population of the same county (Hordaland, Norway) and time period was used for comparison. Information on AMI and IHD events was obtained from hospital patient administrative systems or cardiovascular registries. We estimated incidence rates and standardized event ratios (SER) compared with the general population by Poisson regression.

Results: There was an average annual decline of 1.6% in age- and sex-adjusted AMI incidence rates from 1972 to 2017 (incidence rate ratio 0.984, 95% CI 0.971–0.998). Excess events in RA patients compared with the general population declined on average 1.3% per year for AMI and 2.3% for IHD from 1972 to 2014. The total RA cohort had 49% (SER 1.49, 95% CI 1.30–1.69) more AMI events and 63% (SER 1.63, 95% CI 1.52–1.74) more IHD events compared with the general population. There were no significant excess AMI and IHD events for RA patients diagnosed after 1998 compared with the general population.

Conclusion: Incidence rates and excess events of AMI and IHD in RA patients declined from 1972 to 2017. There were no excess AMI or IHD events in RA patients diagnosed after 1998 compared with the general population.

Background

Rheumatoid arthritis (RA) patients have 1.5 to 2.0 times increased risk of acute myocardial infarction (AMI) and ischemic heart disease (IHD) compared with the general population [1,2]. The AMI risk seems to increase within the first years after RA diagnosis, but is similar to that of the general population before diagnosis [3–6]. Mortality rates for RA patients are about 50% higher than in the general population, and cardiovascular disease (CVD) is the primary cause of death in about 40% of patients [7].

RA involves systemic and non-resolving inflammation that favours the development of atherosclerosis. The AMI risk in RA increases with higher levels of inflammation and higher disease activity [8–12]. Treatment of RA with disease-modifying anti-rheumatic drugs (DMARDs) reduces inflammation and disease activity, and is associated with a lower AMI risk [13–17].

RA treatment has improved vastly over the last two decades, in particular due to the focus on early and aggressive treatment, tight control strategies, and the use of biologic DMARDs for patients with insufficient response to synthetic DMARDs. Several studies have found higher rates of remission and better long-term outcomes in patients with early introduction of DMARDs [18]. This “window of opportunity” may be a critical phase for intervention against the development of atherosclerosis in RA. Several recent studies report a decline in the overall mortality gap between RA patients and the general population in the 21st century, which parallels the improvement in RA treatment [19–24]. However, there

is little information about the AMI and IHD risk in RA patients diagnosed after the introduction of modern RA treatment.

Our aim was therefore to assess if the introduction of improved RA treatment was associated with lower risk of AMI and IHD. We evaluated trends of AMI and IHD incidence in RA patients diagnosed from 1972 to 2013. RA patients were compared with the entire population of the same county and time period to estimate possible excess AMI and IHD events and to adjust for secular changes in the diagnosis of IHD. The estimates of excess risk were stratified by time of RA diagnosis to address possible RA treatment-related changes.

Methods

Study design and setting

We performed a retrospective cohort study of 1821 RA patients compared with the total population from the same county (Hordaland, Norway) during 1972–2014 to investigate possible excess of AMI and IHD events in RA patients. We also evaluated time trends of AMI and IHD events for RA patients from 1972 to 2017.

RA patient cohort

We evaluated all outpatient contacts or hospital admissions with an RA diagnosis at the Department of Rheumatology, Haukeland University Hospital in the period 1972 through 2013. Almost all RA patients in Hordaland county are treated at this hospital. The selection process is shown in figure 1 and explained in detail in the additional file, along with a comparison between the included and excluded RA patients. We obtained consent from 2649 patients through the Norwegian Arthritis Registry (n = 1456) and letters of consent from patients not included in the Norwegian Arthritis Registry (n = 214). Exemption from consent was allowed in patients who were dead (n = 979) by the Regional Committee for Medical and Health Research Ethics. The included RA patients were diagnosed during 1972–2013 by the treating rheumatologist. Most RA patients are in secondary care for several years. We therefore excluded patients with fewer than 5 hospital contacts assuming them as initially misdiagnosed, miscoded or treated at a different institution.

Data on AMI and IHD events in RA patients were obtained from the Western Norway Cardiovascular Registry (WENOCARD) (1972–2006) and from the hospital's patient administrative system (2007–2017) as illustrated in figure 2 [25,26]. We only included events where Hordaland was the current county of residence. Cause of death was obtained from the Norwegian Cause of Death Registry [27]. The Norwegian personal identification number, unique to each Norwegian resident, was used to link the data sources.

Comparison cohort

The entire population of Hordaland county, including RA patients, was used as a comparison cohort. Population counts and data on AMI and IHD events were obtained from WENOCARD (1972–2006) and the Cardiovascular Diseases in Norway project (CVDNOR) (2007–2014) as illustrated in figure 2 [25,26]. The data on the comparison cohort were only aggregated counts and therefore considered to be anonymized. We did not have data beyond 2014 for the comparison cohort. Counts of AMI and IHD events were aggregated by year, sex and 5-year age groups. A description of WENOCARD and CVDNOR can be found in the additional file.

Definition of outcomes

The outcome of our study was AMI and IHD events. Incident events were used to estimate time trends in AMI and IHD, while multiple events were used to evaluate time trends in excess risk compared with the general population, as well as to estimate standardized event ratios (SER).

An incident event of AMI was defined as a hospitalization with AMI (International Classification of Diseases (ICD)-8/9; 410 and ICD-10; I21, I22) as primary or secondary discharge diagnosis or death from AMI (ICD-8/9; 410–414 and ICD-10; I20–I25) without any AMI-hospitalizations prior to RA diagnosis [28]. An incident event of IHD (ICD-8/9; 410–414 and ICD-10; I20–I25) was defined as hospitalization with IHD as primary or secondary diagnosis or death with IHD as the underlying cause of death without any IHD-hospitalizations prior to RA diagnosis.

When counting multiple AMI-events and IHD-events per person a new hospitalization was counted as a new event if it occurred >28 days after the previous hospitalization. If the new hospitalization occurred ≤28 days after the previous it was defined as a part of the previous event [25].

Data on AMI and IHD events for the RA and comparison cohort were collected from different sources, but are all based on the same discharge diagnosis codes from hospitals in Western Norway. A comparison between WENOCARD and CVDNOR showed little deviation of AMI counts in the overlapping time period (1994-2006) of 0-1.06% [29].

Statistics

We estimated a required sample size of 7769 person-years follow-up for RA and non-RA patients to detect a standardized incidence ratio of 1.5 with 95% confidence and 80% power under the assumption of an incidence rate of 50 per 10 000 in non-RA patients.

The RA patients were divided into three cohorts by time period of RA diagnosis according to main RA treatment trends: 1972–1985 (pre-Methotrexate era), 1986–1998 (Methotrexate era), 1999 and onwards (biologic era). Continuous variables are presented as means with standard deviations and categorical

variables as numbers and proportions. Trends were estimated by linear regression for continuous variables, logistic regression for binary variables and ordinal logistic regression for variables with multiple categories. Missing values were excluded from the analyses in table 1.

Time trends in AMI and IHD incidence in RA patients were explored during 1972–2017. Incidence rate ratios (IRR) and 95 % confidence intervals per one year change in calendar time were estimated using Poisson regression with year included as a continuous independent variable and adjustment for age, bmi, serological and smoking status (and sex for total estimates). Person-years were calculated from 1st January the year RA was diagnosed to the first event, death or end of study period (31st December 2017). We also performed a subanalysis of time trends from 2002 to 2017, due to the introduction of troponins in the diagnosis of AMI at the beginning of the 21st century. Missing values for bmi, serological and smoking status were present in less than 5% of cases and replaced by multiple imputation using the mi function in STATA with weight and sex as an additional predictors.

Standardized event ratio (SER) was estimated by Poisson regression (figure 3) from counts of the total and RA population in Hordaland, Norway at the middle of each calendar year. Expected counts from the comparison cohort were used as an offset, stratified by year, sex and 5-year age interval to obtain indirect standardization (suppl). The model was not adjusted for additional variables such as smoking since they were unavailable for the total population. We calculated separate estimates for the total RA cohort and three diagnostic time cohorts for events occurring in the entire period (1972–2014) and for three time periods (1972–1985, 1986–1998 and 1999–2014). Separate estimates were also calculated for men, women and three age groups. There were no missing values in these analyses.

Time trends in excess risk of AMI and IHD in RA patients compared with the general population were explored by Poisson regression during 1972–2014 with year as a continuous variable to estimate event ratio ratios (ERR) for average annual change in SER. Details are presented in the additional file. There were no missing values in these analyses.

We used robust standard errors to calculate 95% confidence intervals when using Poisson regression to adjust for overdispersion. A p-value below 0.05 was considered significant.

Analyses were conducted using Stata Statistical Software (Release 16. College Station, TX: StataCorp LLC) and R version 3.6.3.

Results

Patient characteristics

Age, body mass index (BMI), prevalence of diabetes and use of antihypertensives and statins at the time of RA diagnosis increased across the diagnostic cohorts (table 1).

The total RA cohort had a follow-up time of 23808 person-years from RA diagnosis to death or 31.12.2014, while the diagnostic cohorts (1972–1985, 1986–1998 and 1999–2013) had respectively 5600, 9536 and 8672 person-years of follow-up.

AMI and IHD incidence rates

In total, 240 incident AMI and 327 incident IHD events occurred in the 1821 RA patients from 1972 to 2017 during respectively 25 890 and 24 345 person-years of observation.

There was an average annual decline in the AMI incidence rates of 1.6% (IRR 0.986, 95% CI 0.970–0.999) adjusted for age, sex, bmi, serological and smoking status (table 2). Similarly, adjusted IHD incidence rates declined on average 3.2% per year (IRR 0.968, 95% CI 0.958–0.978). On average, there was an increase in the AMI and IHD incidence in RA patients older than 85 years (table 2), mostly in men. Furthermore, there was no decline in AMI and IHD incidence in women aged 16–64 years. Trends in AMI and IHD incidence in the 2002–2017 subgroup (supplementary table 1) were similar to those in the total period (1972–2017).

Excess AMI and IHD risk

In total, 269 AMI and 1325 IHD events occurred from 1972 to 2014 in the RA cohort, while 35614 AMI and 126974 IHD events occurred in the general population. The overall SER in RA patients compared with the general population was 1.49 (95% CI 1.30–1.69) for AMI and 1.63 (95% CI 1.52–1.74) for IHD from 1972 to 2014. There was no excess risk in patients older than 85 years. When stratifying by diagnostic cohort and year of event (figure 3), significant excess AMI and IHD risks were seen in the total estimates for the two first diagnostic cohorts, but not in the 1999–2013 cohort (AMI: SER 1.05, 95% CI 0.82–1.35; IHD: SER 1.02, 95% CI 0.89–1.16). There was significant excess IHD risk, but no excess AMI risk for patients in the early phase of RA diagnosed 1985–1998. Exclusion of autoantibody-negative patients did not increase the excess risk in the 1999–2013 cohort. Men and women had similar excess risk in total and in the three diagnostic cohorts.

There was an average annual decline in the excess risk of 1.3% for AMI (ERR 0.987, 95% CI 0.972–1.002) and 2.3% for IHD (ERR 0.977, 95% CI 0.69–0.985).

Discussion

In this large and long-term RA-cohort, we found no excess risk of AMI and IHD events in patients diagnosed from 1999 and onwards, while patients diagnosed before 1999 had a significant excess risk compared with the general population. Furthermore, from 1972 to 2014 there was a decline in the excess of AMI and IHD events in RA patients compared with the general population. The excess risk was similar for both genders and autoantibody positive RA patients compared with the total RA cohort. In addition,

we found a significant overall decline in the incidence rates of AMI and IHD among RA patients from 1972 to 2017. However, patients older than 85 years experienced an increase in AMI incidence rates.

Most previous studies have included patients with long-standing RA, diagnosed before the introduction of modern RA treatment, which could explain excess AMI risk found after the year 2000 [1,2,16,30–34]. Two recent studies found an increased risk of AMI for the total RA cohort but not for subgroups of incident RA [35,36]. We similarly found an increased risk of AMI and IHD compared with the general population for the total RA cohort, but not for RA patients diagnosed after 1998. Both Holmqvist and Lindhardsen et al found an elevated risk of AMI in incident RA cohorts diagnosed from 1995 and 1997 to 2006 compared with the general population, but this was before the introduction of the “treat to target” strategy [3,4].

Treatment with methotrexate and biologics is associated with a lower risk of cardiovascular events [13–17]. The increased use of methotrexate and biologics over time is evident in our cohort as shown in a previous study, and could explain the low AMI and IHD risk seen in RA patients diagnosed after 1998 [37]. Probably, the improved drugs and treatment strategies have reduced inflammation-driven atherosclerosis sufficiently to render the IHD risk similar to the general population. However, other possible explanations could be: less use of corticosteroids and NSAIDs; increased focus on primary CVD prevention in RA patients; and less smoking, which is a known risk factor for severe RA and is associated with decreased response to anti-rheumatic drugs [13,34,38].

Our findings are in line with several studies that did not find excess cardiovascular mortality after 2004 [19,21,23,24,39]. The decline in mortality was attributed to improved RA treatment, but could also be due to improved treatment and primary prevention of CVD, which may have influenced RA patients to a greater extent than non-RA individuals. Mortality data tend to underestimate IHD, and hospitalization data are preferable due to a higher positive predictive value (PPV) for AMI [40,41]. Our study corroborates the significant decline in cardiovascular disease in RA patients in the 21st century by using data from hospital records. Overall, there was a decline in AMI and IHD incidence rates in RA patients during the study period. This matches findings in the general population of Norway and other countries in Europe [42–45]. However, we found an increase in elderly RA patients which is likely due to non-RA-related factors since there was no excess risk in this age group. Possible explanations could be a lower threshold for hospitalization of older patients and increased detection of type 2 AMI after the introduction of troponins. Similar findings have been reported in the general population in Denmark and the UK [46,47]. The lack of a declining trend seen in younger women with RA is in accordance with several previous studies of the general population showing an increasing trend in younger women from around 1988 until 2009 [25,48–50].

The main strengths of our study are the long study period of an unselected RA population stratified by time of RA diagnosis and the use of the general population as a comparison cohort. Data from region-wide registries and hospital records have ensured completeness of the outcome variables. The comparison cohort made it possible to adjust estimates of excess risk for changes in definition and diagnosis of IHD over time.

Our study has some limitations. Substantially more patients in our cohort were diagnosed with RA in the latter time period (1999-2013). This could be due to lack of effective RA treatment in the earlier time periods and hence less referrals to secondary care especially for milder forms of RA. It is therefore possible that RA patients diagnosed during the first period had a more serious illness, which could correspond to a higher risk of IHD. We used two different sources for outcomes from 2007 and onwards for the RA and comparison cohort, but both were based on hospital discharge diagnosis codes. Furthermore, we lacked data on smoking status for the comparison cohort, thus we could not adjust the estimates for changes in smoking. Another limitation is the use of recurrent AMI and IHD in comparison to the total population, which are likely less precise outcomes than incident AMI. A study using the Danish National Patient Registry, which is comparable to the registries in our study, found a higher PPV for incident AMI (97%) compared to recurrent myocardial infarction (88%) and IHD (88-93% for stable and unstable angina) from 2010-2012.

Our findings have several clinical implications. Patients diagnosed recently with RA appear to have equal risk of IHD to the general population and should therefore receive similar primary CVD prevention. However, individual considerations should be made by the treating rheumatologist, for instance in cases of severe RA or poor response to RA treatment. Our findings support treatment of RA to a target of remission to avoid RA-related IHD and associated societal costs.

Conclusions

RA patients have historically had an excess risk of IHD compared with the general population. Our study found a decline in IHD and excess risk of IHD from 1972 to 2014 and there was no such excess risk in RA patients diagnosed after 1998. Our findings support early and aggressive treatment of RA and indicate that patients with well-controlled RA may have an IHD risk similar to the general population.

List Of Abbreviations

AMI: Acute myocardial infarction; BMI: Body mass index; CVD: Cardiovascular disease; CVDNOR: Cardiovascular Diseases in Norway project; DMARDs: Disease-modifying anti-rheumatic drugs; ERR: Event rate ratio; ICD: International Classification of Diseases; IHD: Ischemic heart disease; IRR: Incidence rate ratios; PPV: Positive predictive value; RA: Rheumatoid arthritis; SER: Standardized event ratio; WENOCARD: Western Norway Cardiovascular Registry

Declarations

Ethics approval and consent to participate: The study complies with the Declaration of Helsinki approved and was approved by the Regional Committee for Medical and Health Research Ethics, Health Region West (2014/1932). Living RA participants gave consent either through registration in the Norwegian Arthritis Registry or letters of consent. Exemption from consent was allowed in RA patients who were dead by the Regional Committee for Medical and Health Research Ethics.

Consent for publication: Not applicable

Availability of data and materials: The datasets generated and analysed during the current study are not available since the approval by the Regional Committee for Medical and Health Research Ethics does not allow for sharing of de-identified data.

Competing interests: CLA reports grants from Western Norway Regional Health Authority during the conduct of the study. BSF reports attendance of an advisory board meeting by Eli Lilly Norge A.S Customer Meeting Services where travel expenses were paid by the company.

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Authors' contributions: CLA participated in the planning of the study, data collection, analysis and interpretation of the data and writing of the manuscript. BTF participated in the planning of the study, interpretation of the data and writing of the manuscript. TWN participated in the planning of the study, data collection, interpretation of the data and revision of the manuscript. CGG participated in the planning of the study and revision of the manuscript. HM participated in the planning of the study and revision of the manuscript. JI participated in the planning of the study, analysis and interpretation of the data and revision of the manuscript. GST participated in the planning of the study, interpretation of the data and revision of the manuscript. All authors read and approved the final manuscript.

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Disclaimer: The interpretation and reporting of the data are the sole responsibility of the authors, and no endorsement by the Norwegian Cause of Death Registry is intended, nor should be inferred.

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Tables

Table 1: Baseline characteristics of patients with rheumatoid arthritis according to time of diagnosis, Hordaland, Western Norway.

Characteristics of patients	Time of RA diagnosis			p for trend
	1972– 1985 (n = 236)	1986– 1998 (n = 535)	1999– 2013 (n = 1050)	
Women	171 (73%)	388 (73%)	706 (67%)	0.120
Age at RA diagnosis, years	52.9 (13.0)	54.5 (16.3)	56.1 (15.9)	0.005
BMI during follow-up, kg/m ²	24.3 (4.1)	25.2 (4.4)	25.6 (4.5)	< 0.001
Smoking status at RA diagnosis				< 0.001
Missing	27 (11%)	18 (3%)	4 (0%)	
Non-smoker	104 (50%)	268 (52%)	425 (41%)	
Former smoker	35 (17%)	86 (17%)	339 (32%)	
Smoker	70 (33%)	163 (32%)	282 (27%)	
Comorbidities ^a				
Previous AMI	11 (5%)	25 (5%)	54 (5%)	0.760
Previous stroke	2 (1%)	12 (2%)	33 (3%)	0.068
Diabetes	4 (2%)	16 (3%)	68 (7%)	0.007
Angina	15 (6%)	35 (7%)	57 (6%)	0.576
Antihypertensive treatment	24 (10%)	64 (12%)	247 (24%)	< 0.001
Statin treatment	0 (0%)	8 (2%)	131 (13%)	0.002
ACR/EULAR criteria fulfilled	200 (85%)	454 (85%)	933 (89%)	0.079
RF/ACPA positive during follow-up	154 (65%)	326 (61%)	719 (69%)	0.372
ESR ^b , mm/h	56.1 (32.3)	49.4 (30.9)	43.7 (26.0)	< 0.001
CRP ^b , mg/l				0.584
Missing	227 (96%)	7 (1%)	1 (0%)	
Mean (SD)	29.7 (49.1)	44.7 (44.3)	37.8 (44.2)	
Arthritis on X-ray during follow-up	207 (88%)	370 (69%)	425 (41%)	< 0.001

Values in the table are mean ($\pm$ SD) for continuous characteristics and N (%) for discrete characteristics. ACPA, anti-citrullinated protein antibodies; ACR, American College of Rheumatology; AMI, acute myocardial infarction; BMI, body mass index; CRP, c-reactive protein; ESR, Erythrocyte sedimentation rate; EULAR, European League against Rheumatism; RA, rheumatoid arthritis; RF, rheumatoid factor.

^aBefore and 1 year after RA diagnosis.

^bThe highest value within 1 year before and 2 years after the diagnosis of RA.

Table 2: Annual change in rates of acute myocardial infarction and ischemic heart disease for RA patients.

Age-adjusted incidence rate ratio (95% CI), 1972–2017			
	Total ^a	Men	Women
All ages			
AMI	0.984 (0.971–0.998)	0.984 (0.961–1.008)	0.984 (0.967–1.002)
IHD	0.975 (0.964–0.986)	0.974 (0.956–0.993)	0.976 (0.962–0.990)
16–64 years			
AMI	0.996 (0.967–1.026)	0.987 (0.951–1.020)	1.006 (0.960–1.056)
IHD	0.985 (0.963–1.007)	0.970 (0.944–0.997)	1.003 (0.965–1.042)
65–84 years			
AMI	0.973 (0.957–0.989)	0.976 (0.947–1.006)	0.972 (0.953–0.991)
IHD	0.971 (0.958–0.984)	0.976 (0.952–1.000)	0.970 (0.954–0.985)
85+ years			
AMI	1.056 (1.003–1.111)	1.118 (0.962–1.299)	1.037 (0.984–1.093)
IHD	1.007 (0.959–1.057)	1.064 (0.974–1.163)	0.991 (0.940–1.046)
Fully adjusted incidence rate ratio (95% CI), 1972–2017 ^b			
	Total ^a	Men	Women
All ages			
AMI	0.984 (0.970–0.999)	0.983 (0.959–1.008)	0.986 (0.968–1.004)
IHD	0.968 (0.958–0.978)	0.964 (0.948–0.980)	0.970 (0.957–0.983)
16–64 years			
AMI	0.997 (0.968–1.028)	0.998 (0.963–1.033)	1.004 (0.953–1.056)
IHD	0.977 (0.958–0.997)	0.970 (0.946–0.995)	0.987 (0.953–1.022)
65–84 years			
AMI	0.971 (0.955–0.988)	0.968 (0.937–1.000)	0.972 (0.953–0.992)
IHD	0.964 (0.953–0.977)	0.961 (0.939–0.983)	0.965 (0.951–0.980)
85+ years			
AMI	1.062 (1.008–1.119)	1.144 (0.981–1.333)	1.039 (0.983–1.098)
IHD	0.985 (0.945–1.026)	1.011 (0.923–1.108)	0.970 (0.925–1.017)

Percent of the average change in rates per year is obtained by subtracting incidence rate ratio from 1.
AMI: acute myocardial infarction; CI: confidence interval; IHD: ischemic heart disease.

^aSex-adjusted analyses.
^bAdjusted for age, year, bmi, serological and smoking status

Figures

Figure 1

Selection of patients with rheumatoid arthritis, Hordaland, Western Norway. NorArthritis, the Norwegian Arthritis Registry; RA, rheumatoid arthritis.

Cohort	Data Source	1972 - 2006	2007 - 2014	2015 - 2017
RA cohort	WENOCARD			
	Hospital PAS			
Comparison cohort	WENOCARD			
	CVDNOR			

Figure 2

Data sources used to identify acute myocardial infarction (AMI) and ischemic heart disease (IHD). CVDNOR, Cardiovascular Disease in Norway; PAS, patient administrative system; RA, rheumatoid arthritis; WENOCARD, The Western Norway Cardiovascular Registry.

Figure 3

Excess AMI and IHD risk in rheumatoid arthritis (RA) patients compared with the general population. The estimates are given for three time periods of events (AMI or IHD) and according to the period of RA diagnosis, given with 95% confidence intervals (CI). Point estimates are standardized event ratios comparing the number of events in the RA cohort to expected number of events calculated from reference rates in the general population and standardized for age, sex and year of the event. Both the RA and

general population were obtained from Hordaland, Western Norway. AMI, acute myocardial infarction; IHD, ischemic heart disease.

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