Cardiovascular disease in patients with osteogenesis imperfecta — a nationwide, register-based cohort study

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A B S T R A C T

Background: Osteogenesis imperfecta (OI) is a hereditary connective tissue disease often due to mutations in genes coding for type 1 collagen. Collagen type 1 is important in the development of the heart and vasculature. Little is known about the risk of cardiovascular disease (CVD) in OI.

Objective: To investigate the risk of symptomatic CVD in OI.

Design: A Danish nationwide, population-based and register-based longitudinal open cohort study.

Participants: All patients registered with the diagnosis of OI from 1977 to 2013 and a reference population matched 5:1 to the OI cohort.

Measurements: Sub-hazard ratios for mitral and aortic valve regurgitation, atrial fibrillation and flutter, heart failure and vascular aneurisms and dissections comparing the OI cohort to the reference population.

Results: We identified 687 cases with OI (379 women) and included 3435 reference persons (1895 women). The SHR was 6.3 [95% CI: 2.5–15.5] for mitral valve regurgitation, 4.5 [95% CI: 1.4–13.9] for aortic valve regurgitation, 1.7 [95% CI: 1.1–2.8] for atrial fibrillation/flutter, and 2.3 [95% CI: 1.4–3.7] for heart failure. The SHRs were not increased arterial aneurisms or dissections.

Limitation: Our results were limited by lacking clinical information about phenotype and genotype of the included patients.

Conclusion: We confirm that patients with OI have an increased risk of CVD compared to the general population.

This held true even when adjusting for factors that are known to contribute to development of these diseases. Our results suggest that the collagenopathy seen in OI may be part of the pathogenesis of CVD in OI.

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1. Introduction

Osteogenesis imperfecta (OI) or ‘brittle bone disorder’ is a rare systemic connective tissue disorder that is largely caused by mutations in the genes related to the biosynthesis of collagen type 1 [1]. The clinical presentation of OI is heterogeneous and ranges from almost asymptomatic to prenatally lethal. Most patients present with blue sclera and multiple fractures after little or no precipitating trauma [2]. OI has a population prevalence of 10.6 per 100,000, and a prevalence at birth of 21.8 per 100,000 [3].

Collagen type 1 is an important constituent of different parts of the cardiovascular system, including the heart valves, chordae tendineae, fibrous rings of the heart, the interventricular septum, aorta, and most other arteries [4,5]. The collagen fibers in the ventricular myocardium contribute to the tensile stiffness and maintain the architecture of the myocytes [6]. Two murine OI models, the Aga2 and OIM, in addition to the bone phenotype also have specific cardiovascular phenotypes [6,7]. Furthermore, homozygote OIM mice have lower collagen area fraction with lower collagen fiber number density in the heart [6].

Valvular regurgitation is a frequently reported cardiovascular disease (CVD) among patients with OI, but most of the current literature...
comprises case reports or small case series [8]. Cross-sectional studies have reported increased aortic root diameter, increased prevalence of diastolic dysfunction, and valvopathies in patients with OI, but most of the included patients were asymptomatic despite cardiovascular pathology [8]. Furthermore, the studies did not describe the burden of other, non-structural, diseases of the heart (e.g. atrial fibrillation or ischemic heart disease) that could bias the results.

The Framingham Heart Study reported a 39% increased risk of new onset atrial fibrillation for each 5 mm increase in the left atrium diameter in patients evaluated by echocardiography [9]. In a non-OI population, the risk of heart failure is closely associated with ischemic heart disease and with increasing age [10]. The reduced amount of collagen type 1 that is seen in OI could result in lower tensile strength and enlargement of both the atria and the ventricles, thus causing atrial fibrillation or flutter and heart failure, independent of other risk factors, at an earlier age than expected. Casuistic reports have been published on arterial dissections and vascular aneurysms in OI, but no cross-sectional or cohort data are currently available [8].

Individual-level data on Danish births, deaths, migration, and all contacts to the healthcare system are available for research. Discharge diagnoses for all in-hospital stays and all surgical procedures have been registered since 1977 and are available through the National Patient Register (NPR). Since 1994, diagnoses for all emergency department and outpatient clinic contacts have also been included in the NPR [11]. Information on dispensed medical prescriptions has been recorded in the Danish National Prescription Register (DNPR) on an individual level since 1994 [12]. These registers are linked by a unique personal identification number (CPR) issued to all Danish residents [13].

1.1. Study objectives and hypothesis

We aimed to investigate the risk of CVD in patients with OI compared to the general population using the Danish health registers. We hypothesized that patients with OI would have increased risk of CVD, especially valvopathies, atrial fibrillation, and cardiac failure as well as aneurysms and dissections, independent of other risk factors for CVD. The hypothesis is summarised in Fig. 1.

2. Methods and study population

The present study is part of a large register-based study on OI in Denmark. Results on mortality and causes of death have been published elsewhere [14].

2.1. Study design

The study is a nationwide population- and register-based open-cohort study that included all patients registered with an OI diagnosis in the Danish health registers and a matched reference population. The participants were followed from 1977 to 2013.

2.2. Data sources

Statistics Denmark Division of Research Services supplied anonymized data (Project reference number: 704542). The Statistics Denmark Division of Research Services is a government institution that administers most of the Danish health registers used in research.

2.3. Study participants

Patients: We included all patients registered in the National Patient Register (NPR) with an ICD-8 (756.59) or ICD-10 (Q78.0) diagnosis of OI between January 1st 1977 and December 31st 2012. Reference population: Five persons, matched to each patient with OI by gender, birth year and month, were randomly selected from the National Persons Register. To limit misclassification, the Statistics Denmark Division of Research Services limited the data so that reference individuals could not be first or second degree relatives to the patients with OI, nor had they later acquired an OI diagnosis.

2.4. Outcomes, variables, and registers

Table 1 shows the different variables, the relevant register and the corresponding diagnosis or codes for each outcome. The date of diagnosis was defined as the date of the first entry into the NPR or the date of first dispensed prescription of relevant medication.

To safeguard patient anonymity, we were not permitted to tabulate outcomes in any group with fewer than 3 events. For such low frequency events we shall use the term <3.

2.4.1. Primary outcomes

Information on mitral valve regurgitation, aortic valve regurgitation, atrial fibrillation/flutter, heart failure, vascular dissections, and aneurysms were extracted from the NPR through diagnosis or procedure codes.

2.4.2. Secondary outcomes — ischemic CVD

Information on ischemic heart disease or arteriosclerotic disease was extracted as discharge diagnoses through the NPR. The use of any platelet aggregation inhibitor or nitroglycerin was taken as an indicator of underlying arteriosclerotic disease, and extracted information on use of these drugs through the DNPR. Information on any coronary surgery was extracted from the NPR and interpreted as indicative of ischemic heart disease.

2.4.3. Secondary outcomes — risk factors for CVD

Information about diabetes was extracted through the NPR as ICD-8 or ICD-10 diagnosis for diabetes, but we also considered any registration of dispensed anti-diabetic medication in the DNPR as indicative of diabetes. Information about dyslipidemia was extracted through the DNPR as use of any lipid-lowering drugs or through the NPR as any ICD-8 or ICD-10 diagnosis for dyslipidemia. Information about hypertension was extracted through the DNPR as use of any antihypertensive drugs or through the NPR as any ICD-8 or ICD-10 diagnosis for hypertension. Lastly, information about non-steroidal anti-inflammatory drug (NSAID) use was extracted through the DNPR as a dispensed prescription of any NSAID.

2.4.4. Demographic data

Information about time of death was extracted from the Danish Causes of Death Register. Data on migration were extracted from the CPR register.

2.5. Exposure

As OI is a congenital disease, we defined all identified patients to be at risk from OI-related CVD from birth, even if their OI diagnosis was made nominally at a later stage in life. The participants were followed until death, migration from Denmark, or the end of the observation period.

2.6. Confounders

2.6.1. Surveillance bias

The NPR only registers diagnoses related to hospital visits, and not visits to the general practitioner (GP). Patients with OI are followed in four adult care centers and two pediatric care centers in Denmark, and are likely to be registered in the NPR for non-OI related diseases as well. As only some of the cardiovascular conditions included in this study need hospital care and pre-surgical evaluations usually include ECG, the result may be over-representation of certain diseases in the OI cohort if we only relied on NPR data. We therefore defined that a patient had a given disease if they were either registered in the NPR and/or had been dispensed relevant medication registered in the DNPR (see Table 1).

2.6.2. Register bias — observation period

The registers used in this study do not cover the same period, but have overlapping years of observation. The NPR covers the period 1977–2013, the DNPR cover 1994–2013, the National Persons Register was started in 1969 cover all inhabitants of Denmark. When using registers with a relatively short observation period, we risk underestimating the number of events. Furthermore, patients may enter the register some time after being diagnosed with a disease. We have corrected for this potential bias by defining outcomes equally for all participants and extracting the data from the same sources. Ibuprofen as a 200 mg tablet is an over-the-counter drug in Denmark, and as such is not registered in the DNPR. We thus risk underestimating the NSAID use in both groups.

2.6.3. Bias by pre-existing CVDs and risk factors for CVDs

Other CVDs and risk factors for CVDs, which are less likely to be influenced by the amount or quality of the available collagen type 1 (e.g. ischemic heart disease), could influence our results. Fig. 1 shows the relationships between the variables included in our study. We ran both an unadjusted model to describe the overall excess risk in patients with OI and an adjusted model to estimate the excess risk directly attributable to OI after correcting for differences in clinical risk factor profile.

2.6.4. Competing risks bias

We have previously shown that patients with OI have increased risk of premature death compared to the reference population (unpublished but accepted for publication JBMR). The competing risk of death may result in a lower number of outcome events in the OI cohort. We therefore used the Fine and Gray [15] competing risk regression to calculate the SHR between the OI cohort and the reference population.
2.6.5. Immortal time bias
To limit immortal time bias, i.e. where patients emigrate from Denmark and may be diagnosed with one of the outcomes but are not registered in the Danish health registers, we censored any participants who had emigrated.

2.7. Statistical analysis
All statistical analyses were done using Stata® 14.1 (StatCorp, USA). We present the cumulative risk of having a given outcome over time and estimating the time to an event per participant. Data are presented as mean [± 1 SD], median [interquartile range, or range], number of events and percent of the population, as appropriate. Sub-hazard ratios (SHRs) are presented as the SHR between the OI cohort and the reference population, accepting that if the proportional sub-hazards assumption held, then the coefficients would be constant with time, and the time interactions should not be statistically significant.

We adjusted models for preselected variables as described in Fig. 1 on the rationale that these variables were not associated with OI itself, but increased the risk of the primary outcomes. The unadjusted model will show any increased risk of CVD that can be attributed statistically to OI itself.

We adjusted the SHR estimations for mitral regurgitation and atrial fibrillation or flutter for 1) pre-existing use of platelet aggregation inhibitors, 2) pre-existing use of nitroglycerin agents, 3) any pre-existing diagnosis of acute myocardial infarction or arteriosclerosis, and 4) any pre-existing procedures to the coronary arteries (percutaneous coronary interventions) AND/OR coronary by-pass surgery — thus adjusting the analysis for ischemic heart disease. We accept that we corrected for proxy measures for ischemic heart disease, but wanted an adjusted model to take into account high-risk patients that may have had silent ischemic cardiovascular disease or silent ischemic myocardial infarctions — where no information about their ischemic heart disease would have been registered in the NPR.

We adjusted the models for evaluating the SHR for heart failure for 1) the same pre-existing use of antihypertensive drugs, and 2) pre-existing diagnosis of diabetes mellitus AND/OR any use of antidiuretic drugs, thus adjusting for the increased risk of aneurisms and vascular dissections in hypertension and the decreased risk seen in patients with diabetes.

The models evaluating the SHR for vascular aneurisms and dissections were adjusted for 1) any pre-existing use of antihypertensive drugs, and 2) pre-existing diagnosis of diabetes mellitus AND/OR any use of antidiuretic drugs, thus adjusting for the increased risk of aneurisms and vascular dissections in hypertension and the decreased risk seen in patients with diabetes.

The assumption of proportional sub-hazards was tested by introducing a time-varying coefficient, observing the interaction with time with the grouping variable (OI or reference population), accepting that if the proportional sub-hazards assumption held, then the coefficients would be constant with time, and the time interactions should not be statistically significant.

We used Persons chi-squared to test for differences in categorical variables between the two populations. We corrected for multiple testing using the Bonferroni correction and accepted a p-value of below 0.003 as significant (as we tested 16 between-group differences in prevalence of different CVDs, surgical treatment of CVDs or risk factors for CVDs).
2.8. Ethical considerations

The study was approved by the Danish Data Protection Agency. The investigators were blinded to the identity of the patients and the reference population. The study was not a clinical trial and thus did not require ethics committee approval according to Danish law. To ensure participant confidentiality, results are not shown if the number of participants in a subgroup was under three. The study was approved by Statistics Denmark (project 704542).

3. Results

We identified 687 patients (379 women), of whom 112 died during the observation period, and 3435 persons (1895 women) in the reference population, of whom 257 died during the observation period.

The median follow-up for the primary outcomes was 23,588 [range: 23,497–23,645] person years in the OI group and 120,005 [range: 119,931–120,104] person years in the reference population. The baseline characteristics are summarized in Table 2.

3.1. Secondary outcomes (other CVDs and risk factors for CVD)

Table 3 shows the number of patients registered with each of the included CVDs and risk factors for the CVDs included in this study. The OI cohort had an increased use of antihypertensive drugs and a higher proportion of patients registered with a hypertensive discharge diagnosis in the NPR compared to the reference population (28.1% vs. 21.6%, p < 0.001). Patients with OI had increased use of prescription NSAIDs compared to the reference population (57% vs. 47%, p < 0.001). There was no increased prevalence of ischemic heart disease in the OI cohort.

3.2. Main outcomes

Table 4 shows the number of events in each group and the subhazard ratios between the OI cohort and the reference population for both the adjusted and unadjusted models, for all participants and by gender. The cumulative incidence function, defined as the probability

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**Table 2**

Baseline characteristics.

<table>
<thead>
<tr>
<th></th>
<th>OI cohort</th>
<th>Reference population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of participants [N]</td>
<td>687</td>
<td>3435</td>
</tr>
<tr>
<td>Female participants [N, %]</td>
<td>379 (55%)</td>
<td>1895 (55%)</td>
</tr>
<tr>
<td>Median age when entered into registers</td>
<td>0 [IQR: 0–65.4]</td>
<td>0 [IQR: 0–65.4]</td>
</tr>
<tr>
<td>Median age at end of observation</td>
<td>33.6 [IQR: 15.5–53.8]</td>
<td>33.5 [IQR: 17.1–53.8]</td>
</tr>
<tr>
<td>Median follow-up time per primary outcome</td>
<td>23,588 [range: 23,497–23,645]</td>
<td>120,005 [range: 119,931–120,104]</td>
</tr>
</tbody>
</table>

The table shows the baseline characteristics of the two populations. IQR = interquartile range.
that a particular outcome had occurred before a given time, is shown for each main outcome in Fig. 2.

### 3.2.1. Mitral valve regurgitation

Eleven patients (1.6%) with OI (median age at diagnosis 63 years, IQR 40–69) and 8 patients (0.2%) (median age at diagnosis 75 years, IQR 65–89) in the reference population were registered with a mitral valve regurgitation diagnosis. The unadjusted SHR was 6.7 [95% CI 2.8–16.2] p < 0.001. Proportionally more patients with OI than participants in the reference population were surgically treated for aortic valve regurgitation, but after correcting for multiple testing, this difference was not statistically significant (4 (0.6%) vs 5 (0.2%), p = 0.025).

### 3.2.2. Aortic valve regurgitation

Six patients (0.9%) with OI (median age at diagnosis 42 years, IQR 33–69) and 6 patients (0.02%) in the reference population (median age at diagnosis 56 years, IQR 42–68) were registered with an aortic valve regurgitation diagnosis (unadjusted SHR 4.5 [95% CI 1.4–13.9] p = 0.01). Proportionally more patients with OI than participants in the reference population were surgically treated for aortic valve regurgitation, but after correcting for multiple testing, this difference was not statistically significant (4 (0.6%) vs 5 (0.2%), p = 0.025).

### 3.2.3. Atrial fibrillation or atrial flutter

There was an increased risk of atrial fibrillation or flutter when comparing patients with OI to the reference population (adjusted SHR of 1.6 [95% CI 1.0–2.7] p = 0.049). The median age at diagnosis was 64 years.
In our study, the frequency of mitral and aortic valve regurgitation was low. Only 1.3% of the women and 1.6% of the men in the OI cohort were registered with a mitral valve regurgitation diagnosis, and less than 1% of the total OI population was registered with aortic valve regurgitation. In a Norwegian cross-sectional echocardiography study of 99 adults with OI and a mean age of 43.9 years [± 12.3], Radunovic et al. [16] found that 57.5% of patients had mild mitral regurgitation and 7.1% had moderate mitral regurgitation, while 10.1% had mild aortic valve regurgitation and 10.1% had moderate aortic valve regurgitation. In an Italian cross-sectional study, Migliaccio et al. [17] included 40 clinically asymptomatic NYHA class I patients with OI in a cross-sectional echocardiography study, and found that 38 patients had valvular regurgitation without specific valvular structural alterations. The lower numbers seen in our study could be due to some of the valvular pathologies being asymptomatic and thus not diagnosed. Secondly, we included the total population of registered OI patients — thus also including children. Our findings are more in line with the results of a Canadian cross-sectional echocardiography study that included 109 patients with OI with a mean age of 27 years (range 1–75), where the authors reported clinically discernible valvular dysfunction in 4 (3.7%) patients [18].

4. Discussion

We present data from a nationwide, register-based cohort study that includes all patients registered with an OI diagnosis in the Danish health registers between 1977 and 2013, together with a matched reference population. This is, to our knowledge, the largest cohort study on cardiovascular disease in OI and the first based on registry data from a uniform, tax financed, public healthcare system. The study includes a median of 23,588 (range: 23,497–23,645) person years in the OI group. We found increased risk of mitral valve regurgitation, aortic valve regurgitation, heart failure, and arterial fibrillation or flutter in patients with OI, even after correcting for known risk factors for these diseases.

4.1. Valvular CVD in OI

The median age at diagnosis was 58 years (IQR 44–69) in the OI cohort and 70 years (IQR 62–78) in the reference population. Correcting for ischemic heart disease did not influence the SHR. Analyzing the results in women alone, SHR was not significantly above 1.0 in women with OI compared with women in the reference population.

3.2.4. Heart failure

The median age at diagnosis was 58 years (IQR 44–69) in the OI cohort and 70 years (IQR 62–83) in the reference population. The unadjusted between-group SHR was 2.3 [95% CI 1.4–3.7] After adjusting for confounders for heart failure, there was a significant higher prevalence of heart failure in the total OI population, with a between-group SHR of 2.4 [95% CI 1.5–3.8], p < 0.001. Four percent of the women in the OI cohort and 1.7% of the reference population were registered with a heart failure diagnosis in the NPR (adjusted SHR 2.5 [95% CI 1.4–4.6], p = 0.003). The same figures for men were 1.0% vs. 0.2% (adjusted SHR 2.4 [95% CI 1.2–5.0], p = 0.015).

3.2.5. Vascular dissections and aneurisms

Nine patients with OI (1.3%) and 29 (0.8%) of the reference population were registered with a vascular dissection or aneurism diagnosis in the NPR. Also, there were no significant differences between the two groups regarding the prevalence of surgery on peripheral arteries, aorta and its main branches, or cerebral aneurisms.

(IQR 50–71) in the OI cohort and 70 years (IQR 62–78) in the reference population. Correcting for ischemic heart disease did not influence the SHR. Analyzing the results in women alone, SHR was not significantly above 1.0 in women with OI compared with women in the reference population.

Fig. 2. The between-group cumulative incidence function — as predicted by the between-group, unadjusted Fine and Gray competing risk regression models. The cumulative incidence function was defined as the probability that a particular outcome had occurred before a given time and can be considered as the difference in risk of having the event in question. The OI cohort is depicted as a dashed line, and the reference population as a solid line.
4.2. Heart failure in OI

We saw an increased cumulative incidence of heart failure in patients with OI from the age of 40 years (Fig. 2), and 4.1% of the patients were registered with a heart failure diagnosis in the NPR. Migliaccio et al. [17] found similar ejection fraction between patients with OI and healthy controls, but reported that 95% of OI patients had diastolic dysfunction. Radunovic et al. [19] found that despite the left ventricle systolic and diastolic functions being within normal range, they were significantly lower in the OI population than in the control individuals. The increased SHR was statistically independent of ischemic heart disease.

4.3. Atrial arrhythmias in OI

Relatively more patients with OI than controls were registered with an atrial fibrillation or flutter diagnosis in our cohort. This increased risk was only seen in men. Radunovic et al. [19] found no patients with atrial fibrillation or flutter in their cohort of 99 patients with OI.

Atrial fibrillation and flutter may be under-diagnosed in the Danish health registers, as the conditions can go undetected. The positive predictive value of atrial fibrillation and/or atrial flutter diagnosis in the NPR has been reported to be 92.6% (95% CI: 88.8–95.2%) [20], but no information about the sensitivity of the NPR has been reported (i.e. the % of patients with atrial fibrillation who are registered in the NPR) [21]. In a British epidemiological study of arterial fibrillation, 2.0% [95% CI 1.6–2.4] of participants randomly selected from the general population were diagnosed with atrial fibrillation [22]. This is comparable to the 1.8% patients with an atrial fibrillation or flutter diagnosis found in the control population.

4.4. Arterial dissection or aneurism in OI

Seven men and fewer than 3 women had a vascular dissection or arterial aneurism during the observation period. A literature review including 70 patients with OI from 63 case reports or small case series, showed that 13 patients were described with aortic dissection or aneurism [8]. The reason for this difference can partly be explained by publication bias of the case reports. No cross-sectional studies have systematically evaluated the incidence of vascular abnormalities in OI. Hortop et al. [18] found that the ratio of the observed to the expected incidence bias of the case reports. No cross-sectional studies have systematically evaluated the incidence of vascular abnormalities in OI. Hortop et al. [18] found that the ratio of the observed to the expected incidence of the NPR has been reported to be 92.6% (95% CI: 88.8–95.2%) [20], but no information about the sensitivity of the NPR has been reported (i.e. the % of patients with atrial fibrillation who are registered in the NPR) [21]. In a British epidemiological study of arterial fibrillation, 2.0% [95% CI 1.6–2.4] of participants randomly selected from the general population were diagnosed with atrial fibrillation [22]. This is comparable to the 1.8% patients with an atrial fibrillation or flutter diagnosis found in the control population.

4.5. Study limitations

Our study was observational and based on register data and thus limited to the available data on diagnosis, surgical codes, and dispensed prescriptions. No information about clinical variables such as height, weight, smoking habits, alcohol consumption, or compliance to medicine is available in the Danish health registers. In a Canadian study including 14 children with OI, none of the participants reached the daily recommendation of physical activity [23]. In the Norwegian cross-sectional study of cardiovascular morbidity in patients with OI, 41% of the patients were current or previous smokers. More OI patients than participants in the reference population had a dispensed prescription for NSAID (56.6% vs. 47.2%, p-value <0.001). It is possible that patients with OI more often than the reference population will use prescription NSAID. Low dose NSAID is sold over the counter in Denmark and will not show up in the DNPR. Several observational studies using Danish health registries have shown increased risk of adverse cardiovascular effects associated with NSAID [24]. However, no differences were found in the proportion of diabetes, dyslipidemia, or ischemic heart disease between the two cohorts. There could furthermore be an increased risk of certain CVDs in the OI cohort due to factors that are undetectable through the NPR registers. We had no information on what had led to the OI diagnosis, and there was no knowledge about the positive predictive value or the sensitivity of an OI diagnosis in the NPR. It is also conceivable that the diagnostic barrier for asymptomatic heart disease could be somewhat lower in patients with OI as they would be assessed at regular intervals by specialist centers for rare diseases or bone specialists.

4.6. Study strengths

This is, to our knowledge, the first nationwide, register-based cohort study focused on cardiovascular disease in OI. The data collected for this study came from a uniform and nationwide tax-financed health care system. The national registers were designed for management and financial control and thus have complete long-term follow-up. The coverage of the NPR is above 99% of all hospital contacts and 95% of all surgical procedures [11]. Studies have shown good concordance in register-based studies and questionnaire studies on drug use, using the DNPR [12]. Lastly the age- and gender-matched reference group of randomly selected participants from the general population strengthened the study.

5. Conclusion

We confirm that patients with osteogenesis imperfecta have increased risk of cardiovascular disease. From the age of 50 years there was a significant increase in cumulative incidence for heart failure, mitral valve regurgitation, aortic valve regurgitation, and atrial fibrillation or flutter in the OI cohort. The sub-hazard ratio remained higher in the OI cohort after adjusting for diseases that can cause valvulopathy, atrial arrhythmia, and heart failure, which is in line with the idea that the decreased collagen type 1 found in OI can cause these diseases. We found no increased risk of vascular dissections, but larger systematic cross-sectional studies including a reference population are needed to further evaluate the risk of vascular abnormalities in patients with OI. We recommend that the follow-up of patients with OI include ECG in adults and an evaluation by echocardiography from the age of 50 years of age.

Conflicts of interest

All authors have completed the ICMJE uniform disclosure form at www.imcje.org/coi_disclosure.pdf and declare no support from any organization for the submitted work; LF received speaker fees from Genzymes, a Sanofi Company, and AstraZeneca; JH received speaker fee from Amgen; BL serves on advisory boards for Merck, Eli Lilly, Amgen, and UCB, she has received speaker fees from Amgen, Merck and Eli Lilly and she has received research funding from Novo Nordisk, Eli Lilly, and Orkla. JG serves on advisory board for Merck, and Novo Nordisk. APH serves on advisory boards for Merck, Eli Lilly, Amgen, and Shire, and she has received research funding from Eli Lilly and speaker fee from Eli Lilly, GSK, Genzyme, Amgen; BA reports grants from Novartis (current), personal fees from Nycomed/Takeda (past, within 36 mo), personal fees from Merck (past, within 36 mo), personal fees from Amgen (past, within 36 mo), and grants from UCB (current), outside the submitted work; and KB reports other from Merck, Sharpe, Dohme, other from Amgen, other from Novartis, and other from NPS, outside the submitted work.

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All authors contributed to the design of the study and the interpretation of the results, and reviewed the manuscript. LF performed the statistical analysis and is guarantor for the study. LF wrote the first draft of the manuscript. All authors accepted the final version of the manuscript. We would like to acknowledge Claire Gudex for proof reading and editing of an earlier version of this manuscript. The study is part of LF’s PhD study and did not receive outside funding.
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