European Heart Journal (2010) **31**, 1000–1006
doi:10.1093/eurheartj/ehp567

Patients with severe psoriasis are at increased risk of cardiovascular mortality: cohort study using the General Practice Research Database

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Received 25 October 2009; revised 14 November 2009; accepted 23 November 2009; online publish-ahead-of-print 27 December 2009

See page 902 for the editorial comment on this article (doi:10.1093/eurheartj/ehq042)

Aims Psoriasis is a common chronic inflammatory T-helper cell-1/17 mediated skin disease. Recent studies suggest that psoriasis, particularly if severe, may be an independent risk factor for atherosclerosis, myocardial infarction (MI), and stroke. We conducted a cohort study using the General Practice Research Database to determine if severe psoriasis patients have an increased risk of cardiovascular (CV) mortality.

Methods and results Severe psoriasis was defined as patients who received a psoriasis diagnosis and systemic therapy consistent with severe psoriasis ($n = 3603$). Up to four unexposed patients without psoriasis were selected from the same practices and start dates for each psoriasis patient ($n = 14\,330$). For every death, the cause was determined by review of the electronic medical record. Severe psoriasis was an independent risk factor for CV mortality (HR 1.57; 95% CI 1.26, 1.96) when adjusting for age, sex, smoking, diabetes, hypertension, and hyperlipidaemia. Overall, severe psoriasis patients experienced one extra CV death per 283 patients per year, even when adjusting for major CV risk factors. The relative risk of CV mortality was modified by age. For example, the RR of CV death for a 40-year-old and 60-year-old with severe psoriasis was 2.69 (1.45, 4.99) and 1.92 (1.41, 2.62), respectively. The findings were robust to multiple sensitivity analyses.

Conclusion Patients with severe psoriasis have an increased risk of CV mortality that is independent of traditional CV risk factors. Additional studies are needed to determine the mechanism of this association and the impact that control of psoriasis has on CV risk.

Keywords Cardiovascular mortality • Atherosclerosis • Risk factors • Psoriasis

Introduction

Psoriasis is a common, chronic inflammatory disease of the skin and joints that affects ~2–4% of the general adult population.[1,2] Psoriasis is associated with impairments in health-related quality of life, even in mild cases, and is associated with excess all-cause mortality in patients with severe disease.[3,4] The cause of psoriasis remains unknown; however, its pathogenesis involves a complex interaction between genetics, the immune system, and environmental exposures.

Recent evidence suggests that chronic psoriasis may be associated with other conditions that are caused, in part, by chronic inflammation.[5] For example, helper T-cells type 1 (Th-1) chronic inflammation characteristic of psoriasis is also central to the pathophysiology of other conditions such as insulin resistance, atherosclerosis, and plaque rupture leading to thrombotic events.[6,7] Patients with psoriasis have increased prevalence of traditional cardiovascular (CV) risk factors such as diabetes,[8] hypertension,[9] metabolic dyslipidaemia,[10] tobacco use,[11] and obesity. Furthermore, even after adjusting for these risk factors, recent epidemiological

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studies support an independent association between psoriasis and myocardial infarction (MI), coronary artery disease, stroke, diabetes, endothelial cell dysfunction, and atherosclerosis.[12–15]

Despite evidence of increased all-cause mortality[4] in patients with severe psoriasis and accumulating evidence of increased prevalence of CV risk factors, there is a paucity of data examining whether psoriasis is associated with increased mortality due to CV disease (CVD) after adjusting for CV risk factors. The purpose of the present study was to determine if patients with severe psoriasis have an increased risk of CV mortality.

Methods

Study population and data source

The study was conducted and is reported based on recommendations of the STROBE statement.[16] The study population was derived from the General Practice Research Database (GPRD), a medical records database in the UK that was established for epidemiological research in 1987.[17] The GPRD is representative of the UK population in terms of age and sex, as well as geographic distribution. Approximately 5% of the UK is represented in this database, and it contains over 9 million patient records with 40 million person-years of follow-up. Over 99% of patients through the National Health Service are registered through their general practitioner (GP) and the database captures both diagnoses and medications. The GPRD has been shown to capture information on diagnoses and treatments from specialists through the GP's electronic medical record.[18] General practitioners received specific training and incurred penalties in order to ensure high quality data. The data are also audited for completeness and a practice receives an up-to-standard (UTS) designation when at least 95% of relevant prescriptions and diagnoses are captured electronically. This database has also been studied in numerous validation studies, including those of psoriasis and CVD, to demonstrate that it captures these outcomes accurately.[1,12]

Time period and age eligibility

Data were obtained between 1987 and 2002 for patients who were 18 or older at the date their person-time began.

Definition of exposure

We defined severe psoriasis patients as those with a diagnostic code of psoriasis, and history of systemic therapy consistent with severe psoriasis. Systemic therapy included phototherapy, psoralen plus ultraviolet A radiation, methotrexate, azathioprine, cyclosporine, oral retinoids (etretinate, acitretin), hydroxyurea, and mycophenolate mofetil. Of note, during the time period that this study was conducted, biologic therapies were not approved for use for psoriasis in the UK. The unexposed population (controls) was composed of patients with no history of a psoriasis diagnostic code.

Sampling of exposed and unexposed cohorts

All patients with severe psoriasis (as defined above) who were age 18 or older at their index date and had at least 1 day of observation time were included. For patients with severe psoriasis, their index date was the first date on or after the first diagnosis of psoriasis in which the patient received a code for treatment consistent with severe disease. For patients without psoriasis, their index date was the date of a medical record entry which was within 60 days of the psoriasis index date. Up to four unexposed subjects who were age 18 or older at their index date were randomly selected for each psoriasis patient, matched on practice, date of registration in the practice, and psoriasis index date (corresponding to a medical record date of the unexposed patient). The matching on dates occurred as follows: registration: ± 90 days (if registration date ≥ 1980, otherwise ± 5 years), index date: ± 60 days. The purpose of matching on practice, registration, and index dates was to ensure that patients with and without psoriasis were evaluated by similar physicians during the same time period to account for potential variations in medical practice and to allow for similar degrees of opportunity for GPs to identify medical conditions in psoriasis and non-psoriasis patients.

Person-time calculation

For severe psoriasis patients, follow-up started at the latest of the date of when the patient could first be defined as having severe psoriasis (e.g. received a treatment code consistent with severe disease), was registered with the practice, or the practice was deemed UTS. For unexposed subjects, follow-up started at the latest date of when the patient was registered in the practice, the index date (matched to the psoriasis index date), and the practice was deemed UTS. For all groups, follow-up ended at the date of death, transfer out of the practice, or end of UTS.

Outcome of interest

The outcome of interest was CV death defined as diagnoses consistent with MI, stroke, peripheral vascular disease, arrhythmia, or left ventricular thrombus entered on or very close to the entry of death. For every death, the cause was determined by review of medical codes on or very near date of death by two physician reviewers blinded to exposure status (R.S.A. and A.L.N.). If there were discrepancies, a third blinded physician reviewer was utilized (J.M.G.). Agreement on cause of death was 96%.

Co-variables of interest

We identified traditional CV risk factors including age, sex, hypertension, diabetes, hyperlipidaemia, and smoking (current, former, never) by the presence of diagnostic codes. Body mass index was directly calculated from available data in the medical record.

Analysis

The sample size was determined by including the maximum eligible number of patients with severe psoriasis based on age criteria. We randomly selected up to four unexposed subjects per patient with psoriasis as additional matching yields minimal increases in statistical power. Data were summarized descriptively. Dichotomous variables were tested with Fisher's exact test. Continuous variables were tested with a *t*-test if they were normally distributed, or with the Wilcoxon test if the data were not normally distributed. We fit age- and sex-adjusted Cox models to determine the overall hazard ratio of CV death in psoriasis patients.[19] When univariate Cox models indicated an association of psoriasis with CV death, we fit additional models with covariates included (described above) as well as models with age and sex interaction terms, to determine if the relative risk of CV death in psoriasis patients was different based on sex or age characteristics. The primary model includes major CV risk factors. Body mass index was recorded in about 69% of patients. Each dichotomous variable in the model was checked for proportionality while adjusting for the other covariates in the model by examining diagnostic log–log plots. We used the Greenland method of external adjustment to determine the degree to which our findings could be explained by an unknown or unmeasured confounder.[20] Multiple sensitivity analyses were performed to test the underlying assumptions of our primary analysis. All analyses were performed using STATA 10.0, and a

P-value of <0.05 was threshold for statistical significance, and $P < 0.10$ for interaction analysis.

Protection of human subjects

This study was approved by the University of Pennsylvania Institutional Review Board and by the Independent Scientific Advisory Committee of the Medicines and Healthcare Products Regulatory Agency of the United Kingdom Department of Health. The study was conducted in accordance with the Declaration of Helsinki.

Results

In this study, we identified 3603 patients with severe psoriasis, and 14 330 matched unexposed patients (*Table 1*). Patients with severe psoriasis patients were slightly older and more likely to be male and have established CV risk factors than patients without psoriasis including hypertension, hyperlipidaemia, tobacco use, Type 2 diabetes ($P < 0.05$ for all). Furthermore, the majority of patients with severe psoriasis were treated with methotrexate (*Table 2*).

The incidence of mortality due to CVD in unexposed subjects and psoriasis subjects is shown in *Table 3*. The frequency of deaths due to CVD was higher in patients with severe psoriasis. The unadjusted overall risk of mortality due to CVD per 1000 person-years was significantly increased ($P = 0.002$) in patients with severe psoriasis patients (8.75, 95% CI 7.18–10.56) compared with unexposed patients (6.19, 95% CI 5.51–6.93). After adjusting for traditional CV risk factors (age, sex, hyperlipidaemia, hypertension, smoking, diabetes), severe psoriasis was an independent risk factor for death due to CVD (HR 1.57; 95% CI 1.26, 1.96) (*Table 4*). On the basis of these analyses, we estimate that each year there is approximately one excess death from CVD per 283 severe psoriasis patients. There was no statistical interaction (also known as effect modification) between psoriasis and sex ($P = 0.99$); however, there was an interaction between psoriasis and age ($P = 0.07$). For example, the adjusted relative risk of CV mortality in a severe psoriasis patient who is 40 years old and 60 years old was 2.69 (1.45, 4.99) and 1.92 (1.41, 2.62), respectively. The adjusted excess risk of CV mortality in a 40- and 60-year-old psoriasis patient was 6.05 deaths/10 000 person-years and 41.30 deaths/10 000 person-years, respectively.

The results were robust to a variety of sensitivity analyses shown in *Table 5*. Body mass index was not included in the primary model

Table 1 Characteristics of study group

Characteristics	Unexposed ($n = 14\,330$)	Psoriasis ($n = 3603$)
Sex (male)	5783 (40.4%)	1750 (48.6%), $P < 0.001$
Age (year)[#]		$P < 0.001$
Mean ± SD	49.7 ± 19.3	52.2 ± 16.7
Median (IQR)	48 (33–65)	52 (39–66)
Diabetes mellitus	737 (5.1%)	270 (7.5%), $P < 0.001$
History of MI	375 (2.6%)	116 (3.2%), $P = 0.052$
History of stroke	268 (1.9%)	89 (2.5%), $P = 0.023$
History of TIA	243 (1.7%)	68 (1.9%), $P = 0.432$
Hyperlipidaemia	842 (5.9%)	250 (6.9%), $P = 0.019$
Hypertension	3049 (21.3%)	858 (23.8%), $P = 0.001$
Smoking		
Never	10 465 (73.0%)	2488 (69.1%)
Current	755 (5.3%)	241 (6.7%)
Former	3110 (21.7%)	874 (24.3%), $P < 0.001$
BMI[a]		
<25	5057 (51.2%)	1025 (42.1%)
≥25 and <30	3291 (33.3%)	860 (35.4%)
≥30	1522 (15.4%)	548 (22.5%), $P < 0.001$
Reason for end of study		
Death	790 (5.5%)	297 (8.2%)
End of UTS	11247 (78.5%)	2860 (79.4%)
Transfer out	2293 (16.0%)	446 (12.4%), $P < 0.001$

Unless notes otherwise, *P*-values are derived using Fisher exact test. MI, myocardial infarction, TIA, transient ischaemic attack, BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); SD, standard deviation; IQR, interquartile range.
[a]Data for BMI were available for 69% of the patients.
[#]Wilcoxon test.

Table 2 Systemic therapies received by patients with severe psoriasis ($n = 3603$)

Systemic therapy	Number of patients with severe psoriasis (%)
Methotrexate	2114 (58.7%)
Psoralen or phototherapy	607 (16.9%)
Azathioprine	582 (16.2%)
Cyclosporine	390 (10.8%)
Etretinate or acetretin	333 (9.2%)
Hydroxyurea	208 (5.8%)
Mycophenolate mofetil	9 (0.3%)

Percentages do not add up to 100 because patients could have received more than one systemic therapy.

Table 3 Incidence of cardiovascular disease mortality in patients with psoriasis compared with patients without psoriasis (unexposed population)

Variable	Unexposed ($n = 14\,330$)	Psoriasis ($n = 3603$)
Follow-up time (year)		
Mean ± SD	3.4 ± 2.8	3.4 ± 2.7
Median (IQR)	2.6 (1.2–5.0)	2.7 (1.2–5.1)
Number of person-years	48 661.8	12 346.3
Number of CVD mortality cases (%)	301 (2.1%)*	108 (3.0%)*
Incidence per 1000 person-years (95% CI)	6.19 (5.51, 6.92)	8.75 (7.18, 10.56)

CI, confidence interval; SD, standard deviation; IQR, interquartile range.
*$P = 0.002$

as its inclusion did not alter the association between psoriasis and CV death and it was captured in only 69% of patients (*Table 5*). Finally, analysing our data using an external adjustment approach suggests that such an unknown or unmeasured confounder would have to be common in the general population (prevalence of 20%), and have a strong association with psoriasis (OR 2.67 or greater) and a very strong association (OR 6.5 or greater) with CV death in order to render our findings null.[20]

Table 4 Unadjusted and adjusted Cox proportional hazard regression models of the risk of cardiovascular disease mortality in severe psoriasis compared with unexposed patients

Covariate	Model hazard ratio (95% CI)
	Severe psoriasis
Unadjusted analysis	
Psoriasis	1.42 (1.14, 1.76)
Adjusted for age and sex	
Psoriasis	1.57 (1.26, 1.96)
Age per year	1.10 (1.09, 1.11)
Sex (male)	1.61 (1.32, 1.95)
Primary model (adjusted for major cardiovascular risk factors)[a]	
Psoriasis	1.57 (1.26, 1.96)
Age per year	1.10 (1.09, 1.11)
Sex (male)	1.54 (1.27, 1.88)
Hypertension	1.25 (1.01, 1.53)
Hyperlipidaemia	0.75 (0.42, 1.34)
Hx of diabetes	2.25 (1.68, 3.02)
Smoking (current vs. never)	1.33 (0.95, 1.86)
Smoking (former vs. never)	1.31 (0.98, 1.74)

Interaction term for sex was not statistically significant ($P = 0.99$), but was for age ($P = 0.07$). CI, confidence interval.
[a]Hypertension, hyperlipidaemia, diabetes, and smoking status.

Discussion

The results of this study demonstrate that patients with severe psoriasis have a clinically significant 57% increased risk of CV death beyond the risk of death associated with traditional CV risk factors. On the basis of our data, a patient with severe psoriasis has an excess risk of CV death attributable to psoriasis of 1 in 283 patients per year. The risk of CV mortality in patients with severe psoriasis was not explained by major cardiac risk factors identified in routine medical practice, suggesting that severe psoriasis may be an independent risk factor for CV death. Moreover, the relative risk of CV death associated with severe psoriasis was highest in younger individuals suggesting a process of accelerated CVD in younger severe psoriasis patients. Therefore, it is of utmost importance that patients with severe psoriasis and their providers are aware of this increased risk and that these patients undergo appropriate risk assessment and implementation of prevention strategies.

The strengths of the current study include the utilization of a large population-based database that is well accepted for CV epidemiological studies and well-validated for psoriasis.[1,9,17,18] In addition, the increased risk of CV death and point estimates were robust to a variety of sensitivity analyses (*Table 5*). We attempted to ensure that we were capturing patients who were seen regularly, minimizing the risk that information bias could explain the findings. In addition, even when patients with highest risk for CV death (i.e. those with history of MI, stroke or transient ischaemic attack, or atherosclerotic disease) were excluded, there was still a 56% increase in CV death associated with severe psoriasis. The results also persisted when examining the risk based on different treatments that theoretically could increase (e.g. cyclosporine, oral retinoids) or decrease (e.g. methotrexate) the risk

Table 5 Sensitivity analysis hazard ratio point estimates

Covariate	*n* Psoriasis	*n* Controls	Model hazard ratio (95% CI)
Primary analysis	3603	14 330	1.57 (1.26, 1.96)
Inclusion of patients with at least 1 GP visit per year on average	3563	13 643	1.54 (1.23, 1.93)
Primary model excluding patients with history of myocardial infarction, stroke, and/or TIA or atherosclerotic disease	3310	13 335	1.56 (1.20, 2.04)
Primary model with exclusion of methotrexate	1489	14 330	2.04 (1.51, 2.74)
Primary model with exclusion of oral retinoids or cyclosporine	2914	14 330	1.51 (1.18, 1.94)
Primary model restricted to patients who received oral retinoids	333	14 663	1.59 (0.97, 2.60)
Primary model with exclusion of psoriatic arthritis	2375	14 330	1.52 (1.19, 1.94)
Primary model with BMI included[a]	2433	9870	1.66 (1.19, 2.30)
Primary model without BMI included in those who had BMI measured[a]	2433	9870	1.64 (1.18, 2.27)
Inclusion of patients with at least 6 months of person time	3246	12 766	1.66 (1.30, 2.11)
Primary model after matching cases to controls by age ($\pm$5 years) and sex[b]	3603	7205	1.59 (1.23, 2.04)

CI, confidence interval; TIA, transient ischaemic attack; GP, general practitioner; BMI; body mass index.
[a]BMI is included in $n = 12\,303$ or 69% of patients.
[b]Two-to-one matching using original controls.

of CVD.[21,22] Thus, these findings suggest that the increased CV mortality is not due to treatment effect. The results also persisted when restricting the severe group to patients treated with therapy specific to severe psoriasis (e.g. oral retinoids), and when excluding patients with psoriatic arthritis suggesting that the findings are associated with severe skin psoriasis as opposed to misclassification with other diseases in which our systemic therapies may be indicated. Our data are consistent with recent studies that demonstrate that psoriasis is an independent risk factor for coronary artery disease,[12–15] stroke,[15,23] and MI.[12,15] Our study builds upon previous findings that severe psoriasis patients have an increased relative risk CV mortality that is highest in younger individuals by evaluating outpatients, as opposed to hospitalized patients while also controlling for major CV risk factors.[24]

Psoriasis is a prototypical Th-1, 17 inflammatory disease, and Th-1 cellular secreted factors (e.g. intracellular adhesion molecule-1, TNF-α) are indeed involved in the pathogenesis of atherosclerosis and MI.[25] Furthermore, given the accumulating evidence of inflammation playing a key role in development, progression, and complications of atherosclerosis,[26] our findings have biological plausibility. Another Th-1 disease, rheumatoid arthritis, has also been shown to be associated with increased risk of MI[27] and multi-vessel coronary disease.[28] Recent studies have shown coronary microvascular dysfunction in patients who have chronic inflammation such as in rheumatoid arthritis or systemic lupus erythematosus.[29] Patients with psoriasis have elevated high-sensitivity C-reactive protein[30] which has been independently associated as a marker for increased risk of CV events.[31,32] Finally, a recent study showed increased CVD defined as coronary artery disease, peripheral arterial disease, and stroke in patients with psoriasis,[15] however this was not population-based and did not evaluate for CV mortality.

In addition to the inflammatory burden driving CAD risk in these disease states, there may be shared genetic risk which contributes as well. Genetics have been shown to play a key role in susceptibility to psoriasis[33] and metabolic disorders, such as diabetes[34] and dyslipidaemia,[35] as well as coronary artery disease.[36] Interestingly, replicated genetic loci identified in psoriasis such as *CDKALI* have been shown to be associated with Type 2 diabetes.[37] Diabetes has long been known to be a potent risk factor for MI,[38] and a shared genetic component between diabetes and psoriasis may contribute to our findings. Recent studies have found that psoriasis is an independent risk factor for developing diabetes and therefore, it is possible that metabolic affects of psoriasis may mediate the association of psoriasis and CVD.[9,39] Furthermore, a gene related to blood cholesterol levels, *APOE4* (apolipoprotein E-4),[40] was recently shown to be associated with psoriasis, and this too may be a shared mechanism for increasing coronary risk through lipid pathways. Interestingly, two key inflammatory signalling molecules, *TNFAIP3* (tumour necrosis factor inducible protein A20) and its interacting protein *TNIP1*[41] were discovered using genome-wide association to be strongly associated with psoriasis. Variation in the *TNFAIP3* gene in mice[42] and in humans[43] has been shown to increase coronary artery disease.

As with all studies, there are important limitations to consider. In database studies, there remains the possibility for misclassification of CV death. If misclassification of CV death is present, such errors would be expected to be non-differential and therefore would bias our results toward the null. Another potential limitation of our study is that we did not examine patients with exclusively incident (new onset) psoriasis. Ideally, an inception cohort study could be performed. However, in diseases such as psoriasis which may not come to medical attention for many years, it is difficult to validly identify truly incident (new onset) cases in a medical records database setting. Finally, although our study suggests that severe psoriasis is an independent risk factor for CV death, it is possible that incomplete measurement of confounders or unknown confounding factors could explain some of the observed association. For example, we did not control for use of specific medications that may alter CV mortality risk, such as angiotensin converting enzyme inhibitors, HMG-CoA reductase inhibitors (statins), and non-steroidal anti-inflammatory drugs. However, our external adjustment analysis reveals that such unmeasured confounding is unlikely to be driving our results.

This study adds to the growing literature suggesting that patients with severe psoriasis are at increased risk of CVD that is not explained by traditional risk factors. This is the first paper to report increased CV mortality in this group of patients while controlling for major cardiovascular risk factors. In this study, severe psoriasis was at least as potent a risk factor for CV death as other major known risk factors such as smoking,[44] hyperlipidaemia,[45] and hypertension.[46] Our results did not show an increase in CV mortality in the presence of hyperlipidaemia, although the results were not statistically significant and therefore should be interpreted cautiously. Although treatment of hyperlipidaemia has been shown to decrease CVD events and subsequent mortality at 1 year,[47] no study has shown that hyperlipidaemia is an independent risk factor for CV death after controlling for age, diabetes, tobacco use, and hypertension. In further analyses (data not shown), when we limited the outcome to only MI, consistent with the literature, hyperlipidaemia was an independent risk factor for MI.

This increase in CVD and mortality is important for clinicians to recognize so that counselling and appropriate screening for CVD and its risk factors in patients with severe psoriasis can be implemented.[48,49] Future studies are necessary to determine how psoriasis should influence cholesterol treatment targets as outlined by guidelines such as Adult Treatment Panel III, in which clinicians are advised to consider emerging CV risk factors in their treatment decisions. Additionally, future studies are indicated to determine what degree of psoriasis severity translates into clinically significant CV risk, as well as to determine if controlling psoriasis results in reduction of CV risk.

Acknowledgements

We are indebted to Jean Liu and Xingmei Wang for their assistance in creating the analytical dataset.

Funding

This work was supported by an unrestricted grant to the Trustees of the University of Pennsylvania from Centocor (J.M.G.), the Psoriasis Research Foundation in Honor of Herman Beerman (J.M.G.) and grant K23AR051125 from the National Institute of Arthritis, Musculoskeletal, and Skin Diseases and grant RO1HL089744 from the National

Heart Lung Blood Institute (J.M.G.). The funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript. N.N.M. is a recipient of the American College of Cardiology Young Investigator Award in the Metabolic Syndrome and grant K23HL097151-01.

Conflict of interest. J.M.G. has grants from Amgen, Pfizer, and Abbott, and is a consultant for Amgen, Abbott, Genentech, and Centocor. The other authors confirm that there are no other potential conflicts of interest.

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CARDIOVASCULAR FLASHLIGHT

doi:10.1093/eurheartj/ehp565
Online publish-ahead-of-print 17 December 2009

A sword-like foreign body lodged in the ventricular septum: a rare complication of percutaneous vertebroplasty

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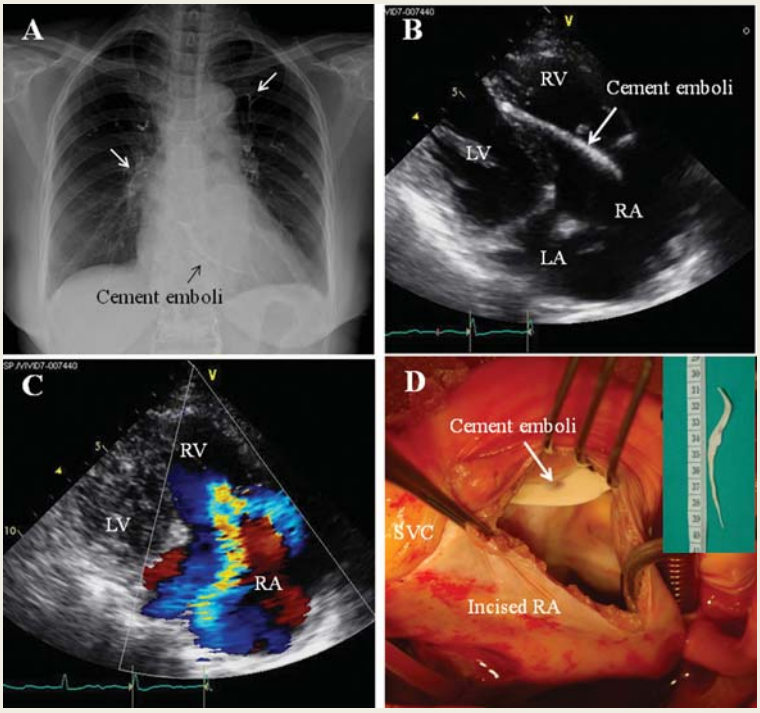

A 76-year-old woman was referred for NYHA functional class III dyspnoea for 1 year. Her medical histories were benign, except hypertension for 5 years. The physical examination revealed irregular heart sounds, a soft holosystolic murmur, and distended jugular veins. An electrocardiography showed atrial fibrillation and a chest X-ray showed multiple, branching radiopacities in both lung fields (white arrows), and a curvilinear dense radiopacity overlying the cardiac silhouette (black arrow; *Panel A*). An echocardiography confirmed a hyperechogenic linear structure (9 cm in length) in the right ventricle with one end in the right atrium through the tricuspid valve and the other end lodged in the ventricular septum (*Panel B*). Colour Doppler echocardiography disclosed severe tricuspid regurgitation (*Panel C*). On further questioning, the patient disclosed a history of percutaneous lumbar vertebroplasty for a compression fracture 5 years ago and the cardiopulmonary embolization of bone cement was diagnosed. The embolized bone cement was surgically removed. The intracardiac embolus was 10 cm in length, destroyed the septal tricuspid leaflet, and nearly perforated the ventricular septum (*Panel D*).

Polymethylmethacrylate (PMMA) is a transparent, thermoplastic substance with various medical applications. Percutaneous vertebroplasty using PMMA is regarded as a safe and effective procedure to treat compression fractures of vertebral bones. The paravertebral venous leakage and pulmonary embolization of PMMA occurs frequently, but is clinically silent in most cases, while cardiac embolization is rare, but may cause serious adverse events.

The abbreviations used are RA, right atrium; LA, left atrium; RV, right ventricle; LV, left ventricle; SVC, superior vena cava.