Psoriasis and the Risk of Major Cardiovascular Events: Cohort Study Using the Clinical Practice Research Datalink

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The association between psoriasis and risk of major cardiovascular (CV) events (myocardial infarction, acute coronary syndrome, unstable angina, and stroke) is unclear. A cohort study with 48,523 patients with psoriasis and 208,187 controls was conducted. During a median follow-up of 5.2 years, 1,257 patients with psoriasis (2.59%) had a major CV event, compared with 4,784 controls (2.30%). In the multivariable analysis, inflammatory arthritis hazard ratio (HR) 1.36 (1.18–1.58), diabetes HR 1.18 (1.06–1.31), chronic kidney disease HR 1.18 (1.07–1.31), hypertension HR 1.37 (1.29–1.45), transient ischemic attack HR 2.74 (2.41–3.12), atrial fibrillation HR 1.54 (1.36–1.73), valvular heart disease HR 1.23 (1.05–1.44), thromboembolism 1.32 (1.17–1.49), congestive heart failure HR 1.57 (1.39–1.78), depression HR 1.16 (1.01–1.34), current smoker HR 2.18 (2.03–2.33), age (year) HR 1.07 (1.07–1.07), and male gender HR 1.83 (1.69–1.98) were statistically significant for the risk of major CV events. The age- and gender-adjusted HRs of a major CV event for psoriasis were 1.10 (1.04–1.17) and for severe psoriasis 1.40 (1.07–1.84), whereas the fully adjusted HRs were attenuated to 1.02 (0.95–1.08) and 1.28 (0.96–1.69). In conclusion, neither psoriasis nor severe psoriasis were associated with the short-to-medium term (over 3–5 years) risk of major CV events after adjusting for known cardiovascular disease risk factors.

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INTRODUCTION

Psoriasis is a chronic skin disorder, now recognized as one of the most common immune-mediated diseases (Griffiths and Barker, 2007) with a prevalence between 0.91% and 8.5% in Western countries (Parisi *et al.*, 2013). The severity of psoriasis can range from a mild disease involving small body surface area to extensive skin involvement and, in many cases, has a major impact on people's quality of life (Rapp *et al.*, 1999; Gelfand *et al.*, 2004; Stern *et al.*, 2004). Psoriasis often coexists with other disorders, perhaps due to chronic inflammation (Griffiths and Barker, 2007), such as obesity (Naldi *et al.*, 2005; Setty *et al.*, 2007), hypertension, hyperlipidemia (Neimann *et al.*, 2006), and diabetes (Lee *et al.*, 2014), which are associated with an increased risk of cardiovascular disease (CVD). The main hypothesis for an association between psoriasis and CVD is that increased systemic inflammation, as occurs in psoriasis, exacerbates other chronic inflammatory diseases including atherosclerosis, which could lead to myocardial infarction (MI) or stroke (Griffiths and Barker, 2007; Boehncke *et al.*, 2011). The possible link between psoriasis and CVD is complex for several reasons: psoriasis is associated with unhealthy lifestyles (increased likelihood of smoking, little physical activity, and obesity; Nijsten and Wakkee, 2009); a higher prevalence of CVD risk factors (such as, diabetes, hypertension, and hyperlipidemia (Neimann *et al.*, 2006)); and therapies for psoriasis that may increase (e.g., ciclosporin (Nijsten and Wakkee, 2009)) or decrease (e.g., methotrexate (Westlake *et al.*, 2010)) the CVD risk; all aspects which may confound the association between the two disorders.

Conflicting evidence exists regarding the relationship between psoriasis and CVD. A number of studies have

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Abbreviations: ACS, acute coronary syndrome; BMI, body mass index; CPRD, Clinical Practice Research Datalink; CVD, cardiovascular disease; IMD, index of multiple deprivation; MI, myocardial infarction; ONS, Office for National Statistics

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suggested an increased risk of fatal and non-fatal CVD events in patients with psoriasis after controlling for several major CVD risk factors (Mallbris *et al.*, 2004; Gelfand *et al.*, 2006; Ludwig *et al.*, 2007; Kaye *et al.*, 2008; Gelfand *et al.*, 2009; Mehta *et al.*, 2010; Ahlehoff *et al.*, 2011, 2012; Lin *et al.*, 2011; Li *et al.*, 2012; Dregan *et al.*, 2014). In contrast, other studies have concluded that psoriasis is not an independent risk factor for CVD (Brauchli *et al.*, 2009; Wakkee *et al.*, 2010; Stern and Huibregtse, 2011; Dowlatshahi *et al.*, 2013). A recent systematic review of epidemiological studies suggested a possible association between severe psoriasis and CVD but acknowledged that the majority of studies failed to adequately adjust for important risk factors (Samarasekera *et al.*, 2013). Inflammatory arthritis, a common co-morbidity in patients with psoriasis and a recognized risk factor for CVD (Han *et al.*, 2006; Symmons and Gabriel, 2011; John and Kitas, 2012), has rarely been considered as a possible confounder. It is also important to note that, in many studies using electronic medical record databases, severe psoriasis is typically defined by exposure to systemic or biologic therapies, which may also be used to treat inflammatory arthritis. This raises the possibility of misclassification of severe psoriasis when not taking account of the presence of inflammatory arthritis. Furthermore, little consideration has been given in earlier studies to the time-varying nature for the development of risk factors or the severity of psoriasis.

Given these premises, a large population-based cohort study was undertaken in order to investigate whether psoriasis is independently associated with an increased risk of major cardiovascular (CV) events (MI, acute coronary syndrome (ACS), unstable angina, and stroke) when taking into account relevant CVD risk factors.

RESULTS

Between 1994 and 2009, 48,523 patients with psoriasis and 208,187 controls met the inclusion criteria. Table 1 summarizes the demographic characteristics of the included patients. Patients with psoriasis had a higher prevalence of the majority of risk factors compared with the control group at baseline (Table 1) and a higher prevalence of all time-varying risk factors at the end of follow-up except for atrial fibrillation, transient ischaemic attack, and congestive heart failure (Table 2). In particular, inflammatory arthritis was present in 2.39% of patients with psoriasis and 0.98% of the controls at baseline and in 4.69% of the patients with psoriasis and 1.38% of the controls by the end of follow-up. In addition, at baseline, there were 1.03% of patients with psoriasis receiving phototherapy, systemic, or biologic therapies, which increased to 4.29% patients by the end of follow-up. Of note, 50.62% of patients receiving systemic or biologic therapies also had a diagnosis of inflammatory arthritis by the end of follow-up. Methotrexate was the most commonly used systemic treatment used in patients with psoriasis (Table 3).

During a median follow-up of 5.2 years, 1,257 patients with psoriasis (2.59%) had a major CV event, compared with 4,784 controls (2.30%). The unadjusted incidence rate of a major CV event per 1,000 person-years was higher in the psoriasis group than the control group (4.13 per 1,000 person-years (95% confidence interval (CI): 3.91–4.36) and 3.87 per 1,000 person-years (95% CI: 3.76–3.98), respectively; Table 4). Investigating the assumption of proportionality by using Schoenfeld residuals revealed time-varying effects for hypertension, transient ischaemic attack, atrial fibrillation, and gender. However, allowing these variables to have different effects for the first 3 years of follow-up compared with the later follow-up removed the non-proportionality ($P=0.12$). The age-and gender-adjusted hazard ratio (HR) of major CV events associated with the presence of psoriasis was 1.10 (95% CI: 1.04–1.17), but this was attenuated and became nonsignificant in the multivariate model (HR 1.02 (95% CI: 0.95–1.08)). The presence of severe psoriasis was associated with an increased risk of major CV events in the age-and gender-adjusted analysis (HR 1.40 (95% CI: 1.07–1.84)), but in the fully adjusted model the HR was above 1 but not significant (HR 1.28 (95% CI: 0.96–1.69)). In the multivariate analysis, the following risk factors (inflammatory arthritis HR 1.36 (95% CI: 1.18–1.58); diabetes HR 1.18 (95% CI: 1.06–1.31); chronic kidney disease HR 1.18 (95% CI: 1.07–1.31); hypertension HR 1.37 (95% CI: 1.29–1.45); transient ischaemic attack HR 2.74 (95% CI: 2.41–3.12); atrial fibrillation HR 1.54 (95% CI: 1.36–1.73); valvular heart disease HR 1.23 (95% CI: 1.05–1.44); thromboembolism HR 1.32 (95% CI: 1.17–1.49); congestive heart failure HR 1.57 (95% CI: 1.39–1.78); depression HR 1.16 (95% CI: 1.01–1.34); current smoker HR 2.18 (95% CI: 2.03–2.33); age (year) HR 1.07 (95% CI: 1.07–1.07); and male gender HR 1.83 (95% CI: 1.69–1.98)) were significantly related to the risk of major CV events (Table 5), whereas hyperlipidemia was not (HR 1.04 (95% CI: 0.96–1.11)). A fully adjusted model with an interaction between psoriasis or severe psoriasis and age was fitted; however, the interaction terms were nonsignificant ($P=0.40$ or $P=0.25$, respectively) and for this reason were not included in the final model.

Results from sensitivity analyses did not change the main findings. Similar results were obtained when adjusting the model for different set of risk factors (Supplementary Table S1 online) or when including body mass index (BMI) and index of multiple deprivation (IMD) as additional risk factors in the multivariate model (Table 6). Likewise, results from the analyses of patients with at least one general practice visit per year, patients with at least 6-month follow-up, or results that took into account patients exposed to methotrexate, ciclosporin, or oral retinoids were consistent with the main findings (Table 6). Finally, a nested analysis including patients from the Clinical Practice Research Datalink (CPRD) linked to the Office for National Statistics (ONS) mortality data and patient-level socioeconomic status (IMD) also yielded similar results to the main findings (Table 6).

DISCUSSION

Our findings suggest that patients with psoriasis have an increased prevalence of comorbidities associated with CVD; however, neither psoriasis nor severe psoriasis was significantly associated with the short-to-medium term risk (over 3–5 years) of major CV events when taking into account other established risk factors for CVD. In particular, the risk of a