Background—The concept that venous thromboembolism (VTE) and atherosclerosis are 2 completely distinct entities has recently been challenged because patients with VTE have more asymptomatic atherosclerosis and more cardiovascular events than control subjects. We performed a meta-analysis to assess the association between cardiovascular risk factors and VTE.

Methods and Results—Medline and EMBASE databases were searched to identify studies that evaluated the prevalence of major cardiovascular risk factors in VTE patients and control subjects. Studies were selected using a priori defined criteria, and each study was reviewed by 2 authors who abstracted data on study characteristics, study quality, and outcomes. Odds ratios or weighted means and 95% confidence intervals (CIs) were then calculated and pooled using a random-effects model. Statistical heterogeneity was evaluated through the use of $\chi^2$ and $I^2$ statistics. Twenty-one case-control and cohort studies with a total of 63,552 patients met the inclusion criteria. Compared with control subjects, the risk of VTE was 2.33 for obesity (95% CI, 1.68 to 3.24), 1.51 for hypertension (95% CI, 1.23 to 1.85), 1.42 for diabetes mellitus (95% CI, 1.12 to 1.77), 1.18 for smoking (95% CI, 0.95 to 1.46), and 1.16 for hypercholesterolemia (95% CI, 0.67 to 2.02). Weighted mean high-density lipoprotein cholesterol levels were significantly lower in VTE patients, whereas no difference was observed for total and low-density lipoprotein cholesterol levels. Significant heterogeneity among studies was present in all subgroups except for the diabetes mellitus subgroup. Higher-quality studies were more homogeneous, and significant associations remained unchanged.

Conclusions—Cardiovascular risk factors are associated with VTE. This association is clinically relevant with respect to individual screening, risk factor modification, and primary and secondary prevention of VTE. Prospective studies should further investigate the underlying mechanisms of this relationship. (Circulation. 2008;117:93-102.)

Key Words: atherosclerosis • risk factors • thrombosis • veins

Clinical Perspective p 102

In previous studies, only obesity has consistently been demonstrated to be an independent risk factor for venous thromboembolic events.\textsuperscript{7,8} Recently, observational studies also have reported a positive association between diabetes and deep vein thrombosis,\textsuperscript{9} arterial hypertension and the risk of pulmonary embolism,\textsuperscript{10} and dyslipidemia and VTE.\textsuperscript{11,12} Elevated levels of triglycerides and low high-density lipoprotein (HDL) seem to increase the risk of VTE, whereas increased HDL levels may protect against VTE.\textsuperscript{12,13} Finally, we recently reported on the association between the metabolic syndrome, a cluster of risk factors for atherosclerosis, and unprovoked deep vein thrombosis.\textsuperscript{14}

From a laboratory perspective, an association between venous and arterial events is plausible because they share common characteristics such as activation of platelets and coagulation.\textsuperscript{15} A number of conditions, including the an-
tiphospholipid syndrome and hyperhomocysteinemia, predispose to both venous and arterial events.16–19 This potential association between VTE, atherosclerosis, and atherothrombosis has obvious clinical implications with respect to screening, risk factor modification, and future therapy. We therefore performed a systematic review of the literature and a meta-analysis to assess the strength of the evidence supporting such an association.

Methods

Study Selection
We identified all published studies that evaluated the prevalence of major cardiovascular risk factors (ie, arterial hypertension, obesity, diabetes mellitus, dyslipidemia, and smoking) in patients with VTE. We conducted a comprehensive literature search of Medline from 1966 through June 2006 and EMBASE from 1980 through June 2006. All searches were carried out without mapping search terms to subject headings. For the first search, text key words were “deep vein thrombosis,” “pulmonary embolism,” and “venous thromboembolism” and excluded “infant,” “newborn,” and “fetus.” The results of this search were combined with the results of a subsequent search. Terms used in the last search were “arterial hypertension,” “blood pressure,” “diabetes mellitus,” “cholesterol,” “triglyceride,” “diabetes,” “hyperglycemia,” “impaired glucose tolerance,” “obesity,” “overweight,” and “smoking.” The results of the combined search were limited to studies of humans published in English. The list of articles was reviewed independently by 3 investigators. When multiple articles for a single study had been published, we used the latest publication and supplemented it, if necessary, with data from the earlier publications. In addition, a manual review of references from primary or review articles was performed to identify any additional relevant studies. We contacted the authors for missing and additional unpublished data. Only studies within which the diagnosis of VTE was objectively confirmed (ie, ultrasonography or computed tomography for deep vein thrombosis and computed tomography, magnetic resonance imaging, or ventilation/perfusion scan for pulmonary embolism) that had a control group were included in the final data set. We excluded all studies in which the entire population of patients with VTE had a concomitant, known, major risk factor (eg, studies carried out in patients undergoing major surgery or trauma and studies involving pregnant women only). The agreement between reviewers for study selection was assessed by the \( \kappa \) statistic.20,21

Data Extraction
Data extraction was performed by 2 investigators, and the results were compiled. Disagreement was resolved by consensus and by opinion of a third author if necessary.

Using a standardized data extraction form, we collected the following baseline characteristics for cases and control groups: lead author, publication year, study design, sample size, mean age, variation in age, and sex. One or more of the following risk factors was collected in each study: number and proportion of patients and controls with systolic and/or diastolic arterial hypertension, hypercholesterolemia, hypertriglyceridemia, diabetes mellitus, obesity, and cigarette smoking. If information on the proportion of patients with and without the risk factor was not available, mean levels and standard deviations were extracted for both cases and controls.

Validity and Study Quality Assessment
We developed a priori criteria to assess study quality.

1. Study design. Prospective cohort studies were considered to be of higher quality than retrospective cohort studies. Case-control studies that were specifically designed to assess the influence of risk factors on the occurrence of VTE were considered to be of higher quality than studies that used a nested case-control design either by identifying cases with VTE by hospital discharge registers or by using existing patient registries.
2. Quality of measurement of risk factors. Studies that adequately reported methodology of measurement of risk factors were considered to be of higher quality than studies that just reported results.
3. Method of patient enrollment. Studies with consecutive patient enrollment were considered to be of higher quality than those with nonconsecutive enrollment.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Statistical Analysis
We used Review Manager (RevMan, version 4.2 for Windows, Oxford, England; The Cochrane Collaboration, 2003) to pool data for each risk factor. The odds ratio (OR) and 95% confidence interval (CI) were calculated for each study, and results were compared through the use of a random-effects model (DerSimonian and Laird22 method). When only mean values and SDs for a certain risk factor were provided, we calculated the weighted mean differences (WMD) between cases and controls. Statistical heterogeneity was evaluated with the \( \chi^2 \) and the \( I^2 \) statistics, which assess the appropriateness of pooling the individual study results.23 The \( I^2 \) value provides an estimate of the amount of variance across studies resulting from heterogeneity rather than chance. Sensitivity analyses were based on the quality of the studies to assess the robustness of our primary results. We subsequently excluded articles in which risk factors were reported instead of actually measured; we then excluded all retrospective cohort studies and case-control studies that were derived from registries or discharge files. For each step, we assessed statistical heterogeneity.

Results

Study Characteristics
Our initial search yielded 1949 potential literature citations (Figure 1). Of these, 1913 were excluded after scanning titles and abstracts, leaving 36 citations for further evaluation. The interobserver agreement for the study selection was excellent \((\kappa=0.98)\). In 4 studies, no comparable data were provided.10,24–26 Three studies did not have a control group,9,27,28 whereas in 2 studies, VTE was diagnosed at postmortem examination.29,30 Of the remaining 27 studies, 2 were excluded because no objective diagnosis of VTE was made,31,32 and 3 studies were excluded because they described the same study group.33–35 Additional data were requested from the authors of 2 studies but obtained for only 1 study.3 Thus, 21 studies were included in the meta-analysis1,2,7,11–13,36–50 with a total of 63,552 patients.

The number of patients in each report ranged between 86 and 21,680 (the Table). The mean patient age varied widely, depending on the inclusion criteria for these studies. Six studies investigated patients <55 years of age,1,12,36,40,41,43,50 Four of the studies involved only patients >45 years of age.1,7,37,48 The mean age of the other studies ranged between 42 and 70 years.11,13,38,39,42,64–47,49 As far as sex was concerned, 8 studies investigated only women,11,36,39–41,43,48,50 5 of these in the range of 15 to 50 years of age,36,40,41,43,50 In 3 studies, only men were included.7,12,37

All 4 cohort studies were prospective,1,7,48,49 with a duration of follow-up between 5.6 and 26 years.7 Follow-up was nearly complete in 2 studies,7,48 whereas in the study by Frederiksen et al,49 65% of the original cohort were followed up. The Longitudinal Investigation of Thromboembolism
Etiology (LITE) study derived data from the Atherosclerosis in Communities Study (ARIC) and the Cardiovascular Health Study (CHS), with complete follow-up in 86% and 95% of patients, respectively. All studies included healthy subjects. Seventeen studies were case-control studies,2,11–13,36–47 Eight were designed to evaluate risk factors for VTE.2,11,12,38,42,44,45,47 Nine studies used either hospital discharge data13,36,39,40,46 or data from registries.37,41,43,50 In 2 studies, only patients with deep vein thrombosis were included.38,44

In only 4 of the 8 incident case-control studies, consecutive patients were enrolled.2,38,44,45 In all but 1 study,49 controls were matched for age. Comparison of the prevalence of cardiovascular risk factors between patients with unprovoked VTE and provoked VTE was not possible given the limited number of studies for which this information was available.

Body Mass Index

Fifteen studies investigated the influence of body mass index (BMI) on the occurrence of VTE: 12 case-control studies11–13,36–40,42,44,45,50 and 3 cohort studies.7,48,49 In 2 studies, SDs were not provided, and these studies were excluded from analysis.7,39 Overall, the studies included 3665 patients with VTE and 31 138 controls. Patients with VTE had a higher mean BMI than controls (WMD, 1.99 kg/m²; 95% CI, 1.51 to 2.47), regardless of whether they were cohort or case-control studies. Statistical heterogeneity among the studies was significant (I² = 79.6%; P < 0.0001) but was present only in the case-control studies. In the studies in which the measurement of BMI was adequately described,11,13,36,37,40,42,45,48,50 the WMD for BMI was 1.73 kg/m² (95% CI, 1.49 to 1.97) higher in the patients with VTE, again with significant heterogeneity (I² = 83.9%; P < 0.00001). However, when we also excluded lower-quality case-control studies, the 3 remaining studies11,42,45 showed no statistical

<table>
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<th>Source</th>
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<th>Study Design</th>
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<th>Women, %</th>
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<td>Case-control</td>
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heterogeneity (WMD for BMI, 2.52 kg/m²; 95% CI, 1.95 to 3.09; I² = 110%; P = 0.74).

Nine studies evaluated the effect of obesity (BMI ≥ 30 kg/m²) on VTE: 8 case-control studies and 1 cohort study with 8125 thrombosis patients and 23 272 controls (Figure 2). Obesity was diagnosed in 8.3% of the cases compared with 3.6% of the controls (OR, 2.33; 95% CI, 1.68 to 3.24), with clear statistical heterogeneity among the studies (I² = 84.5%; P < 0.00001). In the 6 studies in which BMI was adequately measured, the OR was 2.00 (95% CI, 1.72 to 2.32), still with significant heterogeneity (I² = 71.0%; P = 0.004). Five of these studies were of high quality and obesity was associated with an OR of 1.84 (95% CI, 1.55 to 2.18; I² = 69.2%; P = 0.01).

![Figure 2. The influence of obesity (BMI > 30 kg/m²) on VTE.](image)

Hypertension

Ten studies reported or measured blood pressure to evaluate the effect of hypertension on VTE: 7 case-control studies and 3 cohort studies with 12 813 thrombosis patients and 29 742 controls (Figure 3). Patients with hypertension had a slightly higher risk of VTE (OR, 1.51; 95% CI, 1.23 to 1.85), with statistical heterogeneity among

![Figure 3. The influence of hypertension on VTE.](image)
the studies ($I^2=52.4\%; P=0.03$). When we restricted our analysis to studies that adequately reported the measurement of blood pressure, ie, 3 case-control studies$^{2,11,39}$ and 2 cohort studies,$^{1,7}$ the effect of hypertension on VTE disappeared (OR, 1.21; 95% CI, 0.92 to 1.52), without statistical heterogeneity ($I^2=46.8\%; P=0.11$). Analysis of the highest-quality studies did not change the results. A positive association between blood pressure and VTE was found only in the study by Tsai et al,$^1$ which classified hypertension as $>140$/90 mm Hg. The other studies used higher cutoff values ($>160$/90 mm Hg) and found no effect (Figure 3).

### Diabetes Mellitus

Nine studies evaluated the effect of diabetes mellitus on VTE: 6 case-control studies,$^{2,12,37,39,40,43}$ and 3 cohort studies,$^{1,48,49}$ with 5990 thrombosis patients and 50 367 controls (Figure 4). Overall, a 1.4-fold increased risk was present for patients with diabetes mellitus (OR, 1.42; 95% CI, 1.12 to 1.77), with no significant statistical heterogeneity among the studies ($I^2=15.2\%; P=0.31$). However, this effect was determined mainly by the results of the cohort studies (Figure 4). When the cohort studies and 2 case-control studies of higher quality,$^{1,2}$ were analyzed, the OR for diabetes mellitus was 1.38 (95% CI, 1.04 to 1.83), again without statistical heterogeneity ($I^2=21.4\%; P=0.28$).

### Smoking

Smoking status was reported in 10 studies: 7 case-control studies$^{2,12,36,39,41,43,50}$ and 3 cohort studies$^{7,48,49}$ with 3760 thrombosis patients and 34 520 controls (Figure 5). Overall, smoking had no effect on VTE in both case-control and cohort studies, and statistical heterogeneity was significant (OR, 1.15; 95% CI, 0.92 to 1.44; $I^2=81.6\%; P<0.00001$). Sensitivity analysis of 4 studies$^{2,7,48,49}$ also showed no relation between smoking and VTE (OR, 0.93; 95% CI, 0.59 to 1.47; $I^2=60.4\%; P=0.06$). From these studies, it was not possible to discriminate between the numbers of cigarettes and the influence on VTE.

### Total Cholesterol

Eleven studies reported total cholesterol levels; 8 were case-control studies,$^{11–13,38,40,42,45,47}$ and 3 were cohort studies.$^{1,7,49}$ The SD was not provided in 1 study, which was excluded from analysis.$^7$ Mean levels of total cholesterol were not significantly related to VTE (Figure 5). In 8 of 10 studies, measurement of fasting cholesterol levels was adequately reported.$^1,7,49$ The SD was not provided in 1 study, which was excluded from analysis. The results did not change when these 8 studies were analyzed. Significant statistical heterogeneity was present for both analyses ($I^2=94\%; P<0.000001$ for both analyses).

Four case-control studies used cutoff levels for hypercholesterolemia,$^{2,13,43,47}$ with a total number of 1660 cases and 6233 controls. The definition of hypercholesterolemia differed among the studies ($>200\text{mg/dL}$, $>240\text{mg/dL}$, and $>256\text{mg/dL}$), hypercholesterolemia was not defined in 1 other study.$^{43}$ Again, no effect of hypercholesterolemia on VTE was seen (OR, 1.16; 95% CI, 0.67 to 2.02; $I^2=76.3\%; P=0.005$).

### Triglycerides

Eleven studies measured triglyceride levels to investigate their effect on VTE: 8 case-control studies$^{11–13,38,40,42,45,47}$ and 3 cohort studies.$^{1,7,49}$ No SD was provided in 1 study, which was therefore excluded from analysis.$^7$ Because the distribution of triglyceride concentrations is generally skewed, we decided not to pool the results of the studies. In most studies, patients with VTE had higher triglyceride levels than controls, with a mean difference of 21.0 mg/dL (95% CI, 11.0 to 31.0) in the case-control studies and 8.6 mg/dL (95% CI, 1.2 to 16.0) in the cohort studies (Figure 7). In 8 studies, fasting
triglyceride levels were adequately measured\textsuperscript{1,11,12,38,40,42,45,47}
In addition, in these studies, triglyceride levels were on average 21.0 mg/dL (95% CI, 10.0 to 31.0) higher in patients with VTE than in controls.

HDL and Low-Density Lipoprotein Cholesterol

Five studies, including 4 case-control studies\textsuperscript{1,2,13,40,45} and 1 cohort study,\textsuperscript{39} measured HDL cholesterol levels in 895 cases and 9841 controls. Figure 8 shows that HDL was inversely related to VTE in patients with VTE than in controls. This relation was stronger after the exclusion of a nested case-control study\textsuperscript{41} (WMD, −3.16 mg/dL; \(I^2=27.8\%\); \(P=0.24\)).

Only 3 studies\textsuperscript{12,41,45} with 237 VTE patients and 272 controls measured low-density lipoprotein cholesterol levels, with no effect on the occurrence of VTE (WMD, 0.37 mg/dL; 95% CI, −16.8 to 17.52) and significant statistical heterogeneity (\(I^2=85.4\%\); \(P=0.001\)).

Discussion

Major Findings

The results of our meta-analysis suggest that major risk factors for atherothrombotic disease also are significantly associated with VTE. These findings strengthen the hypothesis that cardiovascular risk factors also may be directly involved in the pathogenesis of VTE and corroborate the
results of the studies that challenged the common view that atherosclerosis and VTE are 2 completely distinct disease entities.3,4,51,52

Until now, only obesity has been consistently shown to be a minor risk factor for venous thrombosis, whereas conflicting results have been reported for hypertension, dyslipidemia, diabetes mellitus, and smoking. After pooling the results of all available studies, we not only were able to confirm the association between obesity and VTE (OR, 2.33) but also could demonstrate for the first time an association between VTE and diabetes mellitus, hypertension, low HDL cholesterol, and high triglycerides. The estimated ORs for these variables may be less robust than those reported for established major risk factors for VTE such as cancer or surgery. However, cardiovascular risk factors are more common and often coexist, and as is well known for atherosclerotic disorders, their coexistence is associated with an additive causative effect. Thus, given the multifactorial nature of VTE, it is highly likely that the concomitant action of risk factors for atherothrombosis may be responsible for a substantial proportion of VTE in the general population. This is entirely consistent with the recent evidence of an association between the metabolic syndrome, a cluster of cardiovascular risk factors, and VTE.14

Biological Plausibility
What is the biological plausibility of our assumption? The risk of arterial thrombosis in patients with major cardiovascular risk factors is most likely mediated by the presence of an inflammatory state and hypercoagulability. Both increased inflammation and coagulation also may predispose these patients to develop venous thromboembolic events. Obesity, in particular central and abdominal obesity, is associated with increased thrombin formation and decreased fibrinolysis.53,54 Obesity also is associated with immobility, another risk factor for thrombosis. Diabetes mellitus often is associated with increased levels of procoagulant factors and the inhibition of endogenous fibrinolysis.55–60 The results of a population-based study, in which the age-adjusted risk for VTE was found to be >2-fold higher among diabetic patients than in the nondiabetic background population, further support our data.6 In turn, diabetes mellitus and the metabolic syndrome are increasingly recognized as “inflammatory disorders” that lead to dyslipidemia (characterized by high triglycerides and low HDL cholesterol levels), hypertension, and abnormal blood clotting. It is therefore no surprise that these risk factors also predispose to VTE and can be considered part of the underlying disease process that is associated with cardiovascular disease and venous thromboembolism. Dyslipidemia also is associated with hypercoagulability, endothelial dys-
function, and increased platelet aggregation.\textsuperscript{61–63} Observational studies have found a positive association between dyslipidemia and VTE.\textsuperscript{11–13} An association between low HDL cholesterol and recurrent thrombosis has recently been described, further strengthening our findings.\textsuperscript{64} 

Clinical Relevance

The clinical implications of our findings are potentially important. A significant proportion of VTE, between 26\% and 47\%, is currently classified as apparently unprovoked in the absence of major known risk factors such as cancer, trauma, surgery or medical illness, or pregnancy.\textsuperscript{65} Recognition of cardiovascular risk factors, if proven to be relevant for VTE, may substantially lower these numbers and support new strategies for both primary and secondary prevention of venous thrombosis. Indeed, in contrast to hereditary thrombophilias, these risk factors can be ameliorated with appropriate therapy and lifestyle changes. The role of weight loss and antplatelet and lipid-lowering therapy needs to be specifically assessed. Studies evaluating the role of aspirin in the secondary prevention of VTE are currently underway, and preliminary evidence exists that statins may be protective against VTE.\textsuperscript{15} The obvious mechanism for this protective effect is through improving lipid profiles, but another possibility is that statins may have a direct effect on endothelial function and coagulation.\textsuperscript{66} Finally, the reported increased risk of atherothrombosis in these patients further stresses the need for routine evaluation and management of cardiovascular risk.

Study Limitations

Our study has several limitations. A meta-analysis has inherent weaknesses in terms of combining heterogeneous data sets. Our analysis was by necessity restricted to individual risk factors. Therefore, the distinct possibility exists that the strength of association may be weaker with a multifactorial regression analysis. In the present meta-analysis, it was not possible to adjust or stratify for potential confounders. Age, an important risk factor for VTE, is associated with obesity, hypertension, and type 2 diabetes mellitus, as well as being a risk factor for atherothrombotic disease. Although studies included in our analysis enrolled young and old patients, the effect of age on the strength of the association could not be determined. However, when we compared studies that included only young patients with those that enrolled older patients, the effect of major cardiovascular risk factors on VTE was similar. In addition, in studies like LITE,\textsuperscript{1} higher BMI and triglycerides were still associated with VTE after adjustment for age, sex, and race. An additional limitation of our study lies in the fact that the presence or absence of well-established provoking factors for VTE often was not reported in detail; therefore, a separate analysis of the association between cardiovascular risk factors and either unprovoked or provoked VTE was impossible. From our initial hypothesis, it is likely that the causal role of risk factors for atherosclerosis, if any, is more important in the former than in the latter group. Future studies should specifically address this question. Furthermore, almost no information on thrombophilia testing was provided in these studies. The potential impact of antplatelet and lipid-lowering therapy and other antithrombotic medications could not be evaluated. Finally, a chance exists that major cardiovascular risk factors mediated their effect on VTE through atherosclerosis itself. The concomitant effect of coexisting cardiovascular disease could not be assessed in this meta-analysis because information on comorbidity was not uniformly available in the included studies.

Conclusions

Cardiovascular risk factors are associated with an increased risk of VTE. This association between VTE and atherothrombosis has great clinical relevance with respect to individual screening, risk factor modification, and the primary and secondary prevention of VTE. Future prospective studies should further investigate the underlying mechanisms of this relationship.

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Disclosures

None.

References


Ageno et al  Cardiovascular Risk Factors and Venous Thrombosis


**CLINICAL PERSPECTIVE**

Venous thromboembolism and atherosclerotic cardiovascular disease are commonly considered 2 distinct entities with different predisposing risk factors. However, recent studies have suggested that patients with venous thromboembolism may be at increased risk of both asymptomatic and symptomatic atherosclerosis; other studies also have suggested a potential association between major cardiovascular risk factors and venous thrombosis. We have performed a systematic review of the literature and a meta-analysis to assess the strength of the evidence supporting such an association. The results of our study clearly support the hypothesis that major risk factors for atherothrombotic disease also are significantly associated with venous thromboembolism. In particular, we have found a statistically significant association between venous thromboembolism and obesity, diabetes mellitus, low high-density lipoprotein cholesterol, high triglycerides, and arterial hypertension. Although the estimated odds ratios for these variables were less robust than those reported for established major risk factors for venous thrombosis such as cancer or surgery, our findings are clinically relevant because cardiovascular risk factors are more common and often coexist, and as is well known for atherosclerotic disorders, their coexistence is associated with an additive causative effect. The results of our study may open new perspectives in the management of patients with venous thromboembolism, in particular for those patients presenting with an apparently unprovoked event. Recognition of cardiovascular risk factors, if confirmed to be relevant for venous thrombosis, may support new strategies for both primary and secondary prevention. In particular, the role of weight loss and antiplatelet and lipid-lowering therapy needs to be specifically assessed.
Cardiovascular Risk Factors and Venous Thromboembolism: A Meta-Analysis
Walter Ageno, Cecilia Becattini, Timothy Brighton, Rita Selby and Pieter W. Kamphuisen

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