Venous thromboembolism events among RA patients

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ABSTRACT

Background: Rheumatoid arthritis (RA) is associated with an increased risk for venous thromboembolism. However, so far, relatively few and small size-based studies have been conducted. We aimed to investigate the link between RA and venous thromboembolism utilizing a large sample of subjects originating from a large data base. Materials and methods: The study was performed utilizing the medical database of Clalit Health Services, the largest healthcare provider in Israel. We enrolled all patients with RA and age- and gender-matched controls. Chi-square and t-tests were used for univariate analysis and a logistic regression model was used for a multivariate analysis. RA patients were compared to controls regarding the proportion of venous thromboembolic events (defined as deep vein thrombosis, pulmonary embolism or both). Multivariate logistic regression was employed to assess factors associated with thromboembolic events. Results: The study included 11,782 patients with RA and 57,973 age- and gender-matched controls. RA patients had a higher rate of venous thromboembolism events compared with controls (6.92% vs. 3.18%, respectively, p<0.001). RA and mean C-reactive protein levels were found to be independently associated with the proportion of thromboembolic events (OR 2.27 for RA and 1.07 for each 1 mg/dL increment of mean C-reactive protein, respectively). Conclusion: RA and C-reactive protein levels are independently associated with venous thromboembolic events. Physicians should be aware of such findings and have a lower threshold for suspecting detecting such events in patients with RA, mainly those with mean high levels of C-reactive protein.

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ABBREVIATIONS:
RA: Rheumatoid Arthritis
BMI: Body Mass Index
CHS: Clalit Health Services
CRP: C-Reactive Protein
DVT: Deep Vein Thrombosis
IL-6: Interleukin-6
agulant and thrombolytic factors. Mounting evidence state increases the concentration of different pro-co-
factors converge to accelerated inflammation, in which
the detrimental burden carried by patients with RA which
significantly affects their longevity. Interestingly, many
RA patients also have higher rates of traditional risk fac-
tors for atherosclerosis, of which smoking takes a lead
and many of these patients are also less mobile due to
the musculoskeletal outcomes of the disease. All these
factors converge to accelerated inflammation, in which
the coagulation system also plays a role. Life-threatening com-
plications of pulmonary embolism, excessive morbidity
and mortality related to thromboembolism and cardio-
vascular disease are the main factors that contribute to
the detrimental burden carried by patients with RA which
significantly affects their longevity. Interestingly, many
RA patients also have higher rates of traditional risk fac-
tors for atherosclerosis, of which smoking takes a lead
and many of these patients are also less mobile due to
the musculoskeletal outcomes of the disease. All these
factors converge to accelerated inflammation, in which
the coagulation system also plays a role.

Several studies have shown that the RA inflammatory
state increases the concentration of different pro-co-
agulant and thrombolytic factors. Mounting evidence
suggests that the innate immune system and coagula-
tion system share a common evolutionary origin, and ex-
tensive crosstalk exists between inflammatory cytokines
and coagulation factors. Hence, the activation of the
inflammatory cytokine networks may also induce pro-
thrombotic conditions such as endothelial dysfunction,
tissue factor (TF) overexpression, and inhibition of fibrin-
olysis and protein C.

Our goal in this study was to assess the association be-
tween RA and venous thromboembolic events (VTE), using
the database of the largest healthcare provider in Israel.

METHODS
Ethical approval
This study was approved by an institutional ethics com-
mittee in Soroka Hospital, Beer-Sheba, Israel. It was ex-
empted by the ethics committee from signing informed
consent forms.

Patients selection
This study is one of a series of explorative and analytic
studies based on the chronic disease registry of CHS
(Clalit Health Services), the largest healthcare provider in
Israel that covers over 4.4 million enrollees, grossly half
of the Israeli population.

CHS has a comprehensive computerized database with
continuous real-time input from pharmaceutical, medical
and administrative computerized operating systems. The
database contains a chronic diseases registry, based on
data from hospital discharge notes for inpatients and pri-
mary care and expert physicians’ reports for outpatients.
The study was designed as a cross-sectional analysis.
All RA patients in CHS’s database were included in the
study, as well as five age- and gender-matched con-
trols for each RA patient. Data for each patient included
age, gender, socioeconomic status (SES), smoking sta-
tus, body mass index (BMI), previous diagnosis of VTE
(defined as previous diagnosis of deep vein thrombosis
“DVT”, pulmonary embolism “PE” or both), and previously
documented levels of CRP. RA patients were defined
as such when they had at least one documented diag-
nosis of RA, either by community physician or hospital
discharge note. DVT/PE diagnosis was defined in a sim-
ilar fashion. Due to the structure of the database, it was
not possible to determine the etiology of each disorder.
However, the validity of the diagnoses in the registry was
found to be high in previous studies.

CRP levels were represented by a mean value of all mea-
sured laboratory CRP levels for each participant in blood
exams from 2002-2013 (regardless of time and clinical
setting within which the test was taken).

Statistical analysis
We used student’s t-test to test difference between con-
tinuous variables and Chi-Square for categorical vari-
ables. Univariate analysis was conducted to assess the
distribution of different study covariates between patients
with and without VTE.

A logistic regression model was used to test the associ-
ation between RA and VTE while adjusting for age, gen-
der, SES, smoking status and BMI. An additional mod-
el included all of the aforementioned variables, as well
as CRP levels. Point estimates are presented with 95% confidence interval.

Statistical analysis was preformed using R Statistical
Software (version 3.2.2; R Foundation for Statistical
Computing, Vienna, Austria).

RESULTS
The study included 11,782 patients with RA, and 57,973
age- and gender-matched controls (Table 1). As ex-
pected by the epidemiology of RA disease, most of the
patients in our cohort were females (about 77% in both
groups). Of note, smoking was more frequent among RA
patients in comparison with controls, as was high BMI.

Our study revealed that RA patients had a higher rate
of VTE diagnosis compared with controls (6.92% vs.
Table 1. Basic characteristics of study population.

| Characteristic       | Controls            | RA patients       | p value |
|----------------------|---------------------|-------------------|---------|
|                      | N=57,973            | N=11,782          |         |
| Age, Mean±SD         | 60.8±17.0           | 61.1±17.0         | 0.174   |
| Gender: Male         | 13384 (23.1%)       | 2679 (22.7%)      | 0.413   |
| BMI, Mean±SD         | 28.0±6.58           | 28.2±6.21         | 0.003   |
| SES:                 |                     |                   |         |
| Low                  | 22657 (39.2%)       | 4505 (38.3%)      | Ref.    |
| Medium               | 22831 (39.5%)       | 4816 (41.0%)      | 0.009   |
| High                 | 12334 (21.3%)       | 2438 (20.7%)      | 0.831   |
| Smoking              | 16671 (28.8%)       | 3865 (32.8%)      | <0.001  |
| CRP, Mean±SD         | 0.93±1.94           | 1.25±1.43         | <0.001  |
| VTE                  | 1841 (3.18%)        | 815 (6.92%)       | <0.001  |

SD: Standard deviation; BMI: Body mass index, kg/m²; SES: Socioeconomic status; CRP (years 2002-2013), reference range: 0-0.5 mg/dL; VTE: Venous thromboembolism, defined as DVT, PE or both.

3.18%, respectively, p<0.001), of these events in the RA group, 704 were diagnosed with DVT (6%) and 160 with PE (1.4%).

Univariate analysis (Table 2) has shown that RA patients who experienced VTE were older, more likely to be female and had a higher BMI and a higher mean CRP value. RA patients had a high risk of VTE (OR 2.27, CI 2.80-2.47). Surprisingly, smoking was not found to be associated with a history of VTE.

Table 3 (model 1 and 2) demonstrates an independent association of VTE with increasing age and BMI, as well as female gender and RA. In model 2, it is shown that CRP levels were found to be linearly associated with the odds having VTE, regardless of RA.

DISCUSSION
Cardiovascular disorders are well documented to coexist in RA patients; this association is believed to be high-
ly related with the degree of the inflammatory process. Studies to date have focused mainly on arterial athero-
sclerotic manifestations such as myocardial infarction
and increased carotid artery stenosis, as targets for diag-
nosis and therapeutic interventions.\textsuperscript{1,12-15} Studies on the role of RA and its systemic inflammation in VTE are not as common and are now emerging.

Our data exhibited a significant association between RA
and VTE, showing a twofold increase in the frequency
of VTE among RA patients. Our results match those of
other reports. Chung et al.\textsuperscript{16} have published a popula-
tion-based ten-year-cohort study from Taiwan. Out of the
23.74 million people in their cohort, there were 29,238
RA patients (77% women, mean age of 52.4 years),
matched with 116,952 controls. The risk for developing
DVT and PE in RA patients was increased by 3.36-fold
and 2.07-fold respectively, compared to controls, after
adjusting for age, gender and comorbidities. Other stud-
ies, based on hospitalized patients, also support the con-
cept that RA patients have an increased risk for VTE.\textsuperscript{17,18}

In the Copenhagen General Population Study, conduct-
ed between the years 2004 and 2012, researchers mea-
sured the concentration of immunoglobulin M (IgM) type
RF (Rheumatoid factor) in patients without autoimmune
rheumatic disease or VTE. The main outcome was the
incidence of DVT. In a total of 368,381 person-years, 670
individuals developed DVT. An RF concentration higher
than 110 IU/mL showed the strongest association with
DVT with multivariable adjusted hazard ratios of 9.0 (95% CI 3.1–26) for 1-year follow-up, 4.3 (2.2–8.5) for 5-year follow-up, and 3.1 (1.7–5.6) for up to 32 years of follow-up.\textsuperscript{19}

Our data, similarly to previous studies, may suggest that
there should be a role for thromboprophylaxis in immune
mediated diseases such as RA. From an economical as-
pect, VTE bears a great burden on the health system.
Predicted costs of medical care were found to be 2.5-
fold higher for patients with VTE related to current or re-
cent hospitalizations for acute illness (62,838 US$) when
compared to hospitalized patients without VTE (24,464
US$; P <0.001).\textsuperscript{20} These finding highlight even further the
need for appropriate prophylaxis, as well as the need
to add rheumatic conditions and RA in particular to different
risk models assessing the chances of developing VTE
during hospitalization.

The Padua Prediction Score was created to assess the
risk for VTE in hospitalized patients, and determine their
need for prophylaxis. Although the Padua Prediction
Score identifies acute rheumatologic disorders as in-
creased risk states for VTE, their importance in the scale
is relatively low.\textsuperscript{21} The presented results may imply that
the relative impact of a current inflammatory rheumatic
condition should be assessed differently suggesting a
more substantial contribution to the risk of VTE.

To date, the underlying pathophysiologic pathway for
the association between RA and the hypercoagulable state
is not fully understood, however, several steps in the
inflammatory process have been linked to hypercoag
ulability.\textsuperscript{22-24} Hypercoagulability could be induced by in
flammation, for example via cytokine-induction of tissue
factor (TF) expression, endothelial dysfunction, inhibition
of the protein C system and inhibition of fibrinolysis.\textsuperscript{22-25}

Inflammatory mediators, like CRP, tumour necrosis fac
tor-alpha (TNFα), interleukin-6 (IL-6) as well as comple
ment activation, can trigger TF synthesis in intravascular
cells, such as monocytes and endothelial cells.\textsuperscript{26} As a re
sult of inflammation, endothelial dysfunction and vascular
injury may occur leading to rapid generation of thrombin
at such sites by activating all the arms of the coagulation
system.\textsuperscript{27}

CRP is a hallmark of inflammation and serves as a sur-
rogate marker for the inflammatory activity in many rheu
matic disorders. Many disease activity formulas take in
account the level of CRP as a contributor to the overall
disease activity. Several observations even relate a direct
pathogenic role to CRP in the process of joint erosions

\begin{table}
\caption{Multivariate logistic regression models (with and without CRP) assessing covariates independently associates with VTE.}
\label{table:venous_thromboembolism_events_among_ra_patients}
\begin{center}
\begin{tabular}{|l|c|c|}
\hline
 & Model 1 (without CRP) OR & Model 2 (with CRP) OR \\
\hline Age, per year & 1.04 (1.04-1.04)* & 1.03 (1.03-1.04)* \\
Gender: Male vs. Female & 0.77 (0.69-0.85)* & 0.81 (0.7-0.93)* \\
BMI, per 1 kg/m$^2$ & 1.05 (1.04-1.05)* & 1.05 (1.04-1.06)* \\
SES: Medium vs. Low & 0.94 (0.86-1.03) & 0.92 (0.81-1.04) \\
SES: High vs. Low & 0.91 (0.82-1.02) & 0.93 (0.81-1.07) \\
Smoking & 1.05 (0.95-1.15) & 1.08 (0.96-1.21) \\
RA & 2.23 (2.05-2.43)* & 1.60 (1.44-1.78)* \\
CRP, per 1 mg/dl & - & 1.06 (1.03-1.08)* \\
\hline
\end{tabular}
\end{center}
\end{table}
and bone destruction in RA. CRP was shown to be an inducer of the receptor activator of nuclear factor kappa-B ligand (RANKL). It has a direct effect on the differentiation of osteoclast precursors into mature osteoclasts. Therefore, lowering CRP levels is pertinent to the control and prevention of further joint damage in RA patients. Peters et al. reported that thrombin-activatable fibrinolysis inhibitor levels were significantly higher in RA patients with a high inflammatory state (CRP >10 mg/L) compared to those with lower CRP levels (CRP <10 mg/L). These reports are in line with our findings that demonstrated the higher probability for VTE in RA patients who have higher CRP levels.

In conclusion, our study has shown that RA is independently associated with VTE. CRP levels were also found to be directly related with an increased risk for VTE. Our results challenge the current understanding of this linkage; suggesting that RA should be more commonly known as a risk factor for VTE. This may modify the current manner by which we calculate VTE risk and the need for thromboprophylaxis, as well as our VTE treatment regimens, with a possible effect on the intensity and length of therapy.

**CONFLICT OF INTEREST**

Relationships relevant to this manuscript within the last 3 years: Arnon Cohen received research grants from Janssen, Novartis, AbbVie, and Sanofi. Arnon Cohen served as a consultant, advisor or speaker to AbbVie, Amgen, Boehringer Ingelheim, Dexcel pharma, Janssen, Kamedis, Lilly, Neopharm, Novartis, Perrigo, Pfizer, Rafa, Samsung Bioepis, Sanofi, Sirbal and Taro.

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**AUTHOR CONTRIBUTIONS**

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Shir Azrielant: Wrote paper
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Shmuel Tiosano: Study design and analysis
Yarden Yavne: Wrote paper
Doron Comaneshter: Data collection and study design
Arnon D. Cohen: Data collection and study design
Howard Amital: Study design and paper writing

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