Recurrence and Mortality in Young Women With Myocardial Infarction or Ischemic Stroke: Long-term Follow-up of the Risk of Arterial Thrombosis in Relation to Oral Contraceptives (RATIO) Study

Rates of death in the acute phase of cardiovascular events have decreased, but disease burden remains high in the increasing number of survivors. This finding is particularly important for those affected at a young age. Nevertheless, little information is available on the long-term outcome of young patients who survived a cardiovascular event, especially women. Single disease cohorts have suggested that the risk of cardiovascular disease is driven by recurrence of the index event, but, to our knowledge, this has never been investigated in a single study with multiple index groups. We determined the long-term mortality and subtype-specific morbidity in young women surviving myocardial infarction (MI) or ischemic stroke (IS) compared with a control group.

Methods | A cohort was formed on the basis of the Risk of Arterial Thrombosis in Relation to Oral Contraceptives (RATIO) study, which included consenting women aged 18 to 50 years who survived a first MI or IS from January 1, 1995, through December 31, 1998. Women with no history of arterial thrombosis were recruited as controls. The study was approved by the ethics committees of the participating hospitals. All patients provided written informed consent. Women were followed up to December 31, 2012, by linkage to the Dutch Registry of death certificates and to the Dutch Hospital Data Register (Central Bureau of Statistics) for causes of death and hospital admissions. Data analysis was performed from December 1, 2013, through September 30, 2014. Incidence rates (IRs) and their ratios were calculated for mortality and the first reoccurrence of any acute major cardiovascular event during follow-up. Adjusted hazard ratios (HRs) obtained from Cox proportional hazards regression models were used for comparison with the controls.

Results | A total of 226 women with MI, 160 with IS, and 782 controls (mean age, 42.4, 40.0, and 48.4 years, respectively) were followed up for a median of 18.7 years (interquartile range, 17.5-20.5 years). Mortality rates were 3.7 (95% CI, 2.5-5.4) times higher in patients with MI (IR, 8.8 per 1000 person-years; 95% CI, 6.2-12.3) and 1.8 (95% CI, 1.0-3.5) times higher in patients with IS (IR, 4.4 per 1000 person-years; 95% CI, 2.4-7.6) than in controls (IR, 2.4 per 1000 person-years; 95% CI, 1.7-3.4). This elevated mortality persisted over time (Figure) and was mainly supported by a high rate of deaths from acute vascular events: vascular mortality rate, 3.5 per 1000 person-years (95% CI, 1.9-5.9) in patients with MI, 2.1 per 1000 person-years (95%, 0.8-4.5) in patients with IS, and 0.3 per 1000 person-years (95% CI, 0.1-0.7) in controls.

When counting both fatal and nonfatal cardiovascular events, the IR was highest in patients with IS at 14.1 per 1000 person-years (95% CI, 9.9-19.4), corresponding to an HR of 12.9 (95% CI, 6.7-25.0) compared with controls (Table). The rate was 12.1 per 1000 person-years (95% CI, 8.7-16.2) in patients with MI, with an HR of 9.8 (95% CI, 5.0-19.4) in contrast with controls.

In patients with MI, the rate of cardiac events was 10.1 per 1000 person-years (95% CI, 7.5-13.8) whereas the rate of cerebral events was 1.9 per 1000 person-years (95% CI, 0.8-3.8). In patients with IS, the reverse picture was observed, with a rate of cerebral events of 11.1 per 1000 person-years (95% CI, 7.5-15.9), whereas the risk of cardiac events was 2.7 per 1000 person-years (95% CI, 1.2-5.4).
Discussion | Young women who survived a cardiovascular event have a high long-term mortality and morbidity when compared with the general population. The recurrence pattern is true to type (ie, the recurrence rate for cerebrovascular disease is highest in patients with IS whereas the risk of cardiac events is highest in patients with MI). This finding is supported by studies5,6 that investigated IS and MI separately.

A limitation of this study is the possibility of survival bias owing to the case-control nature of the study cohort, and therefore absolute risks for the period shortly after the first event may have been underestimated. Moreover, procedures and risk factors change over time, which reduces the generalizability of our results, a problem of all long-term follow-up studies. Our findings provide direct insight into the consequences of cardiovascular diseases in young women, which persist for decades after the initial event, stressing the importance of lifelong prevention strategies.

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Author Contributions: Drs Maino and Siegerink had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Acquisition, analysis, or interpretation of data: Maino, Siegerink, Algra, Peyvandi.

Drafting of the manuscript: Maino, Siegerink.

Critical revision of the manuscript for important intellectual content: Siegerink, Algra, Peyvandi, Rosendaal.

Statistical analysis: Maino, Siegerink.

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Administrative, technical, or material support: Maino, Peyvandi.

Study supervision: Siegerink, Algra, Rosendaal.

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Table. Incidence Rates and Hazard Ratios for Cardiovascular Events

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Events, No. (%)</th>
<th>Person-years, No.</th>
<th>Incidence Rate per 1000 Person-years (95% CI)</th>
<th>Hazard Ratio (95% CI)a</th>
<th>Adjusted for Age Only</th>
<th>Adjusted Also for Lifestyleb</th>
<th>Adjusted Also for Diseasec</th>
<th>Adjusted Also for Family History of Cardiovascular Eventd</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any cardiovascular event</td>
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<tr>
<td>Myocardial infarction group (n = 226)</td>
<td>44 (20)</td>
<td>3654</td>
<td>12.0 (8.7-16.2)</td>
<td>12.4 (6.6-23.1)</td>
<td>10.1 (5.14-19.72)</td>
<td>9.6 (4.9-18.9)</td>
<td>9.8 (5.0-19.4)</td>
<td></td>
</tr>
<tr>
<td>Ischemic stroke group (n = 160)</td>
<td>37 (23)</td>
<td>2627</td>
<td>14.1 (9.9-19.4)</td>
<td>15.0 (7.9-28.2)</td>
<td>13.3 (10.0-25.3)</td>
<td>12.8 (6.6-24.7)</td>
<td>13.0 (6.7-25.0)</td>
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<tr>
<td>Control group (n = 782)</td>
<td>13 (2)</td>
<td>14 557</td>
<td>0.9 (0.5-1.5)</td>
<td>1 [Reference]</td>
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<tr>
<td>Myocardial infarction</td>
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<tr>
<td>Myocardial infarction group (n = 226)</td>
<td>37 (16)</td>
<td>3696</td>
<td>10.0 (7.1-13.1)</td>
<td>22.4 (9.3-53.9)</td>
<td>20.9 (8.1-54.0)</td>
<td>18.5 (7.1-48.0)</td>
<td>19.6 (8.0-51.0)</td>
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<tr>
<td>Ischemic stroke group (n = 160)</td>
<td>8 (5)</td>
<td>2941</td>
<td>2.7 (1.2-5.4)</td>
<td>6.5 (2.6-18.7)</td>
<td>6.0 (2.1-17.6)</td>
<td>5.4 (1.8-16.2)</td>
<td>5.6 (1.9-16.8)</td>
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<tr>
<td>Control group (n = 782)</td>
<td>6 (1)</td>
<td>14 588</td>
<td>0.4 (0.2-0.9)</td>
<td>1 [Reference]</td>
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<tr>
<td>Ischemic stroke</td>
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<tr>
<td>Myocardial infarction group (n = 226)</td>
<td>8 (4)</td>
<td>4152</td>
<td>1.9 (0.8-3.8)</td>
<td>3.8 (1.4-10.5)</td>
<td>2.8 (1.0-8.3)</td>
<td>2.8 (1.0-8.2)</td>
<td>2.7 (0.9-8.1)</td>
<td></td>
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<tr>
<td>Ischemic stroke group (n = 160)</td>
<td>30 (19)</td>
<td>2707</td>
<td>11.1 (7.5-15.8)</td>
<td>21.9 (9.6-49.9)</td>
<td>19.1 (8.3-44.3)</td>
<td>18.2 (7.7-42.8)</td>
<td>17.9 (7.6-42.2)</td>
<td></td>
</tr>
<tr>
<td>Control group (n = 782)</td>
<td>7 (1)</td>
<td>14 601</td>
<td>0.5 (0.2-1.0)</td>
<td>1 [Reference]</td>
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</table>

a The hazard ratios are obtained by multivariable Cox proportional hazards regression models and are all adjusted for age.

b The hazard ratios are also adjusted for smoking (ie, smoking at least 1 cigarette a day in the year before the event), alcohol consumption (ie, ingestion of at least 1 glass of alcohol per week), and body mass index (calculated as weight in kilograms divided by height in meters squared).

c The hazard ratios are adjusted for body mass index and additionally for history of diabetes mellitus, hypertension, and hypercholesterolemia.

d The hazard ratios are adjusted for smoking, alcohol consumption, body mass index, and history of diabetes mellitus, hypertension, and hypercholesterolemia and additionally for family history of a cardiovascular event (ie, any acute cardiovascular event before 60 years of age in a first relative).
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Preexposure Prophylaxis Awareness and Use in a Population-Based Sample of Young Black Men Who Have Sex With Men

In the United States, reducing new human immunodeficiency virus (HIV) infections will require a determined focus on primary HIV prevention among young black men who have sex with men (YBMSM), the only group in the United States where HIV incidence has increased over the past decade.1 Through 2011, effective clinic-based HIV prevention interventions that target YBMSM have been virtually nonexistent.2 In 2012, the US Food and Drug Administration approved a preexposure prophylaxis (PrEP) consisting of daily oral tenofovir disoproxil fumarate and emtricitabine. This PrEP has an estimated effectiveness of over 90%,3 and, therefore, an HIV prevention effect potential for several domestic HIV epicenters.4

Methods | The south side of Chicago represents the largest contiguous black community in the United States. Despite the many assets of the south side, this community has a high HIV prevalence. uConnect is a population-based cohort study of YBMSM that examines how sociodemographic, health, behavioral, and social factors drive new methods of HIV prevention, including PrEP.

Using respondent driven sampling (RDS), 622 eligible YBMSM were recruited between June 2013, and July 2014. Study participants were eligible to be interviewed if they (1) self-identified as African American or black, (2) were born male, (3) were between 16 and 29 years of age, and (4) reported oral or anal sex with a male within the past 24 months. The sample was weighted using general probability estimates5 using the RDS package in R (R Foundation). We examined the relationship of a set of sociodemographic, health care engagement, behavioral, and social characteristics with PrEP awareness and uptake.

Results | A final analytic sample of eligible participants (n = 622) was generated through RDS chains of up to 13 waves in length and with a median of 2 recruits per participant. The mean (SD) age of the sample was 22.7 (3.2) years. Approximately 39% of participants had high school- or general education development–level terminal education, and 79.3% reported an income of less than $20 000 per year. Nearly half (48%) of HIV-negative (PrEP-eligible) individuals reported having either some government or private health coverage. At baseline, PrEP awareness among uConnect participants was 40.5%, and 12.1% knew others who had used PrEP. PrEP awareness remained relatively stable over the recruitment period (Figure). Approximately 72.1% of the sample was not infected with HIV, 3.6% of whom had used PrEP. Having a primary care provider, participating in an HIV prevention program or research study, having had an anorectal sexually transmitted infection test, and membership in the House and Ball community, a national network of socially organized “houses” largely comprised of YBMSM and transgender women that has existed in Chicago since the 1930s, were significantly associated with PrEP awareness (Table). Additionally, among PrEP-eligible participants, meeting with an HIV outreach worker within 12 months of being recruited to our uConnect cohort was significantly associated with PrEP awareness (adjusted odds ratio [aOR], 2.02; 95% CI, 1.29-3.16).

Discussion | uConnect is the first study of diverse YBMSM–relevant characteristics and corresponding PrEP engagement from a population-based sample. Low PrEP awareness and uptake among YBMSM parallels earlier HIV treatment disparities. While PrEP is promising, this population-based cohort study illustrates that real-world PrEP use by those with the highest HIV incidence faces major implementation challenges that require purposeful and sustained engagement with black communities inclusive of their health care providers. We find that PrEP awareness is associated with a diverse range of clinical engagement activities among YBMSM. The Affordable Care Act (ACA) represents one potential opportunity to increase such clinical engagement. However, ACA benefits are not recognized in all regions of the United States, and in our cohort, only half of the participants had any type of health care coverage. Ongoing work

![Figure. uConnect Participants Recruited and Percent Aware of PrEP](jamainternalmedicine.com)