




# Incidence of Antiphospholipid Syndrome: Is Estimation Currently Possible?

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## Abstract

Antiphospholipid syndrome is a systemic autoimmune disorder characterized by vascular thrombosis and/or obstetric events in association with persistently elevated antiphospholipid antibodies. Antiphospholipid syndrome is typically considered a rare disease, but the true incidence is uncertain owing to the diverse antiphospholipid antibody-related clinical manifestations, inconsistent definitions of antiphospholipid antibody positivity, under-recognition of the disease, and limited population-based studies. Published estimates of the incidence of antiphospholipid syndrome range from approximately 2 to 80 per 100 000 person-years. A targeted literature review and applied methodology were performed to derive a best available estimate. Significant limitations of the published literature were observed, some of which have been previously reported. The incidence of antiphospholipid syndrome in the United States was estimated to be approximately 7.1 to 13.7 per 100 000 person-years in the general population. Although this estimate is likely more accurate than previously reported estimates, large, contemporary, population-based studies that reasonably adhere to the antiphospholipid syndrome classification criteria are needed to further refine estimates of the incidence of antiphospholipid syndrome.

**Keywords:** Antiphospholipid syndrome, antiphospholipid antibodies, incidence, epidemiology

## Introduction

Antiphospholipid syndrome (APS) is a systemic autoimmune disorder characterized by vascular thrombosis and/or obstetric events in association with persistently elevated antiphospholipid antibodies (aPLs). According to international classification criteria for APS,<sup>1</sup> APS requires: (i) vascular thrombosis (arterial, venous, or small vessel in any tissue or organ) or pregnancy morbidity ( $\geq 3$  consecutive early pregnancy losses; pregnancy loss after 10 weeks gestation; or premature delivery prior to 34 weeks gestation due to preeclampsia or placental insufficiency) plus (ii) aPL, including positive lupus anticoagulant test, and/or anticardiolipin antibodies (aCLs), and/or anti- $\beta_2$  glycoprotein-I antibodies (a $\beta_2$ GPI) in medium to high titers for at least 12 weeks. It is uncommon that both thrombotic and obstetric events occur in the same person with APS<sup>2</sup>; therefore, these manifestations are often considered separately.

Antiphospholipid syndrome is typically considered a rare disease,<sup>3</sup> but the true incidence is uncertain owing to the diverse aPL-related clinical manifestations, inconsistent definitions of aPL-positivity, under-recognition of the disease, and limited population-based studies. Because aPL can be transient, the APS classification criteria require that positive test results be present in "medium to high titer" and be repeated after 12 weeks to confirm APS<sup>1</sup>; however, very few published studies of the incidence of APS have used standardized cutoff values for aPL titers or performed repeated testing.<sup>4</sup> Furthermore, older studies of APS did not assess for all 3 aPLs,<sup>4</sup> because these studies preceded the inclusion of a $\beta_2$ GPI in the APS classification criteria in 2006.<sup>1</sup> Studies of the obstetric manifestations of APS did not consistently assess premature delivery prior to 34 weeks gestation due to preeclampsia or placental insufficiency, and studies of pregnancies that did not result in live births often used imprecise and inconsistent terminology (e.g., spontaneous abortion, miscarriage, fetal loss, and stillbirth) that made interpretation and comparison of results difficult.<sup>4</sup> Lastly, APS commonly causes clinical manifestations that are currently not included in the classification criteria (e.g., thrombocytopenia and livedo<sup>5</sup>), but that nevertheless may be considered when making the clinical diagnosis of APS.<sup>6</sup>

To date, only 1 large population-based incidence study has rigorously and strictly applied the APS classification criteria with respect to qualifying obstetric events, repeat aPL testing, and minimum aPL titers.<sup>7</sup> This study reported an incidence rate of 2.1 per 100 000 person-years but had several important

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limitations. Overall, the sample size was small; the incidence estimate was derived from 33 observed cases over the course of 16 years of observation in Olmsted County, Minn, USA. As acknowledged by the authors, this study, conducted between 2000 and 2015, was significantly limited by the lack of completeness of the clinical evaluation performed at the time of the clinical events. Patients who presented with clinical features consistent with APS but were not assessed for a $\beta_2$ GPI or persistence of aPL could not satisfy the APS classification criteria even if they truly had APS. The number of incompletely evaluated and undiagnosed cases of APS in the study population is hence unknown. Therefore, this study most likely underestimated the incidence of APS and should be considered a minimum estimate.

At the opposite end of the spectrum, a review of 120 studies of aPL positivity associated with thrombotic or obstetric events estimated an incidence of APS of approximately 80 per 100 000 person-years in the USA.<sup>4</sup> This review highlighted the major limitations of the literature; fewer than 20% of the included studies required repeat aPL testing for confirmation, and there was no consistent use of cutoff values for medium or high titer aPL levels (i.e., low titer aPLs were often considered positive). Additionally, there was rarely consideration of other risk factors for thrombotic events (e.g., cardiovascular risk factors for stroke or myocardial infarction in older patients were not considered and all patients were tested for aPL indiscriminately). Because normal healthy persons can have transient or low-titer aPL, this study most likely overestimated the incidence of APS and should be considered a maximum estimate.

Thus, the true incidence of APS very likely lies between the minimum estimate of 2 per 100 000 person-years determined by strict adherence to the APS classification criteria<sup>7</sup> and the maximum estimate of 80 per 100 000 person-years determined by any presence of aPL.<sup>4</sup> This study aimed to perform a targeted review of the published literature to refine the estimated incidence of APS in the USA.

## Methods

A targeted literature review of PubMed was conducted to identify the most relevant publications describing the incidence of APS. Searches were performed using keywords and Medical Subject Headings, title/abstract, and full-text designations. In addition, the reference sections of all identified articles were searched. The search was restricted to full-text articles published in English after 1980. The primary search was conducted in September 2019 and partially updated in January 2021 to assess for recently published articles. When considering which publications to include, priority was assigned to studies that were meta-analyses, systematic reviews, or review articles. When multiple original studies were identified, studies with larger sample sizes, more rigorous methods, more recent publication dates, and more frequently referenced by other publications were prioritized. Only the highest quality studies among the studies identified for each thrombotic or obstetric event were included. No human subjects were involved in this study, and ethics approval was not sought.

An indirect method was used to estimate the incidence of APS (Figure 1). The first step was to identify the published incidence in the general population of the USA for the most common

thrombotic events [venous thromboembolism (VTE), myocardial infarction (MI), and stroke] and all 3 obstetric events included in the APS classification criteria. For the determination of incidence rates, the population of the USA was estimated to be 330 million (www.census.gov). The second step was to estimate the proportion of thrombotic events and obstetric events that may be attributable to APS based upon published studies, including studies of the prevalence of aPL near the time of thrombotic or obstetric events. Because aPL can be identified in asymptomatic individuals and because many identified studies did not properly apply APS criteria by restricting positive results to medium or high titers and by repeating testing 12 weeks later, the estimated proportion of patients with aPL but without APS was subtracted from the proportions reported with aPL in the included studies to determine the proportion of thrombotic or obstetric events truly attributable to APS. The proportion of aPL without APS was determined from general studies of healthy individuals without APS (e.g., healthy blood donors) and controlled studies assessing the specific outcomes (e.g., case-control studies reporting the proportion of persons without thrombotic or obstetric events found to have aPL). The third step was to multiply the incidence of thrombotic and obstetric events by the estimated proportion attributable to APS for each event to determine the event-specific APS incidence rate. The event-specific incidence rates were then summed to determine the incident rates for thrombotic APS, obstetric APS, and overall APS.

## Results

This targeted literature review identified 8 studies that provided best estimates of the

### Main Points

- The true incidence of antiphospholipid syndrome (APS) is uncertain because of diverse APS-related clinical manifestations, inconsistent definitions of antibody positivity, under-recognition of the disease, and limited population-based studies.
- Using a targeted literature review and applied methodology, this study estimated an incidence of 7.1 to 13.7 per 100 000 person-years.
- Large, contemporary, population-based studies that reasonably adhere to the APS classification criteria are needed to further refine estimates of the incidence of APS.

#### Step 1. Estimate Thrombotic and Obstetric Event Rates in the General Population

Events: VTE; MI; stroke;  $\geq 3$  consecutive early pregnancy losses; pregnancy loss after 10 weeks gestation; premature delivery prior to 34 weeks gestation due to pre-eclampsia or placental insufficiency

#### Step 2. Estimate Proportion of Thrombotic and Obstetric Events Possibly Attributable to APS

When studies of APS criteria were unavailable, then the proportion of patients with thrombotic and obstetric events and aPL minus the proportion of patients with aPL in comparator populations without thrombotic and obstetric events was estimated.

#### Step 3. Multiply Incidence of Thrombotic and Obstetric Events By Proportion Possibly Attributable to APS

(e.g., 7 per 100,000 person-years  $\times$  14% = 1.0 per 100,000 person-years)

#### Step 4. Sum Incidence Rates of Thrombotic and Obstetric APS Events

**Figure 1.** Indirect method to estimate the incidence of APS. aPL, antiphospholipid antibodies; APS, antiphospholipid syndrome; MI, myocardial infarction; VTE, venous thromboembolism.

incidence of the thrombotic and obstetric events of interest.<sup>8-15</sup> Three studies were identified that assessed for APS in persons with VTE,<sup>16-18</sup> 6 studies assessed aPL in persons with thrombotic and obstetric events,<sup>4,12,19-22</sup> and 3 studies assessed aPL without APS.<sup>21,23,24</sup> One broadly applicable estimate from a study of healthy blood donors reported the presence of IgG aCL in approximately 6.5% of persons.<sup>23</sup> This estimate was considered in the determination of the proportion of events attributable to APS in the thrombotic and obstetric outcomes.

Table 1 lists the findings of the targeted literature review and the determination of the estimates for the incidence of thrombotic and obstetric APS events.

**Incidence of Thrombotic Antiphospholipid Syndrome Events**

Venous Thromboembolism: Based upon a published review of 11 studies,<sup>8</sup> the annual number of VTE (including deep vein thrombosis (DVT) and pulmonary thromboembolism (PTE) in the USA is approximately 400 000 (approximately 120 per 100 000 person-years in the general population). The proportion of VTE caused by APS is age dependent and drops sharply with

increasing age because of the development of other important risk factors for VTE,<sup>4</sup> and this was considered in the estimate. According to a large prospective registry of patients with VTE,<sup>15</sup> 6% of all VTE episodes were first VTE episodes in patients less than 50 years old without typical risk factors for VTE (i.e., idiopathic or unprovoked VTE), and 31% of all VTE were first, unprovoked events in patients greater than 50 years old. The corresponding incidence rates for first, unprovoked VTE in patients less than and greater than 50 years old are 7 and 37 events per 100 000 person-years in the general population, respectively.

Studies that applied the APS criteria to populations of patients with VTE, rather than assessing only positive aPL results, were identified. A cross-sectional study of data from an oral anticoagulation dosage program reported that 9% of patients less than age 50 with a first, unprovoked VTE met APS criteria.<sup>16</sup> A smaller, prospective study, also of patients less than age 50 with a first, unprovoked VTE, reported that 19% of patients met APS criteria.<sup>17</sup> Taking the midpoint of these 2 reports, an estimated 14% of patients less than age 50 years with a first, unprovoked VTE had APS. Multiplying this

estimate by the incidence of VTE in this patient population (7 per 100 000 person-years) results in an estimate of approximately 1.0 per 100 000 person-years in the general population.

Considering patients older than 50 years, a prospective study of all adult patients with first, unprovoked VTE reported that 9% of patients met APS criteria, irrespective of age (the mean age of patients in the study was 52 years).<sup>18</sup> Because an estimated 14% of patients younger than 50 years old with a first, unprovoked VTE have APS (see above), an estimated approximately 5% of patients older than 50 years had APS, which would be expected to produce the resultant 9% reported for the entire study population of all adult patients.<sup>18</sup> Multiplying this estimate (5%) by the incidence of VTE attributable to this patient population (37 per 100 000 person-years) results in an estimate of approximately 1.9 per 100 000 person-years in the general population.

Adding together the estimates for patients below and above age 50 years, the total incidence of APS manifested by VTE is approximately 2.9 per 100 000 person-years in the general population. If one instead disregards patient age and assumes that overall 9% of all patients with a first, unprovoked VTE have APS,<sup>18</sup> then the estimate is 4.0 per 100 000 person-years (9% of 44 per 100 000 person-years). The true incidence of APS manifested by VTE is likely higher than this estimate because patients may have both a provoking risk factor for VTE and APS concurrently, as has been demonstrated.<sup>15</sup> In fact, the proportion of patients with VTE attributable to APS may be as high as 6% across all patients based upon the median result from 5 studies that conducted confirmatory aPL testing of patients with DVT.<sup>4</sup> If true, this would place the incidence of APS manifested as VTE at approximately 7.2 per 100 000 person-years in the general population (6% of 120 per 100 000 person-years).

Taken altogether, the incidence of APS manifested as VTE is most likely between approximately 2.9 and 7.2 per 100 000 person-years in the general population.

*Myocardial Infarction:* For the determination of the incidence of MI potentially attributable to APS, only events in young adults (less than 45 years old) were considered. Current recommendations advise against aPL testing in patients with MI unless the patient's young age and lack of identifiable risk factors suggest rare etiology.<sup>1</sup> Based upon epidemiologic data from the American Heart Association,<sup>9</sup> the

**Table 1. Estimated Incidence of Potential Thrombotic APS and Obstetric APS Events in the USA**

Potential APS Event	Annual Event Incidence in the USA		Incidence of Event Attributable to APS in General		References
	per 100 000 Person-Years	Percentage of Events Attributed to APS	Population per 100 000 person-years		
Venous thromboembolism	120 (total)	6%	All events		(4, 8, 15-18)
	7 (first VTE, unprovoked, <50 years old)	14%	2.9-7.2		
	37 (first VTE, unprovoked, >50 years old)	5%			
	44 (first VTE, unprovoked, all ages)	9%			
Myocardial infarction	15 (<45 years old)	4.5%-8%	0.7-1.2		(1, 4, 9, 23, 24)
Stroke	15 (<50 years old)	11%-16%	1.7-2.4		(1, 9, 19, 20, 23, 24)
Early pregnancy loss	13	8.5%-11.5%	1.1-1.5		(10-12, 23, 24)
Late pregnancy loss	7	4%-8%	0.3-0.6		(13, 21, 23)
Pre-term delivery due to preeclampsia	4	10%-20%	0.4-0.8		(14, 22)

APS, antiphospholipid syndrome; VTE, venous thromboembolism.

annual number of MI in the USA in persons less than 45 years old is approximately 50 000 (approximately 15 per 100 000 person-years in the general population).

The proportion of MI events associated with aPL was estimated to be approximately 11% based upon a review of 24 studies.<sup>4</sup>

A review of 11 controlled studies of the association between aPL and MI reported aPL detection in 3% of control patients,<sup>24</sup> somewhat lower than the 6.5% reported among healthy blood donors.<sup>23</sup> Considering the estimate for aPL above,<sup>4</sup> approximately 4.5% (11% minus 6.5%) to 8% (11% minus 3%) of MI was attributable to APS among persons less than 45 years old. Although when restricted to 4 studies with confirmatory aPL testing, the aforementioned critical review reported a much higher median value of 18%,<sup>4</sup> suggesting that the proportion of MI attributable to APS may be higher.

Multiplying the incidence of MI in persons less than 45 years old (15 per 100 000 person-years in the general population) by the proportion attributable to APS (4.5%-8%), the estimated incidence of APS manifesting as MI is approximately 0.7-1.2 per 100 000 person-years in the general population.

### Stroke

For the determination of strokes potentially attributable to APS, only events in patients less than 50 years old were considered. Current recommendations state that it is unclear what proportion of ischemic stroke can be attributed to APS, especially in older patients with other risk factors present.<sup>1</sup> The annual number of strokes in the USA in persons less than 50 years old is approximately 50 000 (approximately 15 per 100 000 person-years in the general population) based on epidemiologic data from the American Heart Association.<sup>9</sup>

Regarding the proportion of stroke events associated with aPL, a review of 15 studies assessing laboratory evidence of thrombophilia following ischemic stroke reported that 21% of patients less than 50 years old had aPL.<sup>19</sup> A different review of 38 studies reported a median frequency of aPL of 17.2% among stroke patients less than 50 years old.<sup>20</sup>

A review of 14 controlled studies of the association between aPL and stroke reported aPL detection in 5% of control patients,<sup>24</sup> which was very similar to the 6.5% reported among healthy blood donors.<sup>23</sup> Considering the estimates for aPL above,<sup>19,20</sup> approximately 11%

(17.2% minus 6.5%) to 16% (21% minus 5%) of stroke is attributable to APS among patients less than 50 years old.

Multiplying the incidence of stroke in persons less than 50 years old (15 per 100 000 person-years in the general population) by the proportion attributable to APS (11%-16%), the estimated incidence of APS manifesting as stroke is approximately 1.7-2.4 per 100 000 person-years.

### Incidence of Obstetric Antiphospholipid Syndrome Events

#### Recurrent Early Pregnancy Loss

An estimate of the number of women with recurrent early pregnancy loss in the USA as defined by the APS classification criteria<sup>1</sup> was not identified. However, it has been estimated (presumably by expert opinion) that 1% of all women attempting pregnancy have recurrent early pregnancy loss.<sup>12</sup> Approximately 3.4 million women have intentional pregnancies each year,<sup>10</sup> and this represents approximately 80% of women attempting to become pregnant.<sup>11</sup> Therefore, approximately 4.3 million women are attempting to become pregnant each year in the USA (80% of 4.3 million is 3.4 million). Applying the 1% estimate from above,<sup>12</sup> the estimated number of women with recurrent early pregnancy loss is approximately 43 000 per year (approximately 13 per 100 000 person-years in the general population).

The proportion of recurrent early pregnancy loss associated with aPL was estimated to be approximately 15% based upon a summary of results from 2 studies.<sup>12</sup>

A review of 2 controlled studies of the association between aPL and early pregnancy loss reported aPL detection in 3.5% of control patients,<sup>24</sup> somewhat lower than the 6.5% reported among healthy blood donors.<sup>23</sup> Considering the estimate for aPL above,<sup>12</sup> approximately 8.5% (15% minus 6.5%) to 11.5% (15% minus 3.5%) of early pregnancy loss is attributable to APS.

Multiplying the incidence of recurrent pregnancy loss (13 per 100 000 person-years in the general population) by the proportion attributable to APS (8.5% to 11.5%), the estimated incidence of APS manifesting as recurrent pregnancy loss is approximately 1.1-1.5 per 100 000 person-years in the general population.

#### Late Pregnancy Loss

The number of women with late pregnancy loss is approximately 24 000 per year

(approximately 7 per 100 000 person-years in the general population) based upon the US national fetal death data.<sup>13</sup>

The estimated proportion of late pregnancy loss associated with aPL was approximately 11% based upon a population-based case-control study of stillbirth in the USA.<sup>21</sup>

Because 5% of the control patients without late pregnancy loss in the population-based case-control study had aPL,<sup>21</sup> an estimated approximately 6% (11% minus 5%) of late pregnancy loss is attributable to APS. To represent the uncertainty of this estimate derived from a single study, a range of 4%-8% was used to estimate the incidence.

Multiplying the incidence of late pregnancy loss (7 per 100 000 person-years in the general population) by the proportion attributable to APS (4%-8%), the estimated incidence of APS manifesting as late pregnancy loss is approximately 0.3-0.6 per 100 000 person-years.

#### Pre-term Delivery due to Preeclampsia

The number of pre-term deliveries due to preeclampsia is approximately 12 000 per year (approximately 4 per 100 000 person-years in the general population) based upon a review of 2 published studies.<sup>14</sup>

An estimate for the proportion of pre-term deliveries due to preeclampsia associated with aPL was not identified. Published studies did not use the APS classification criteria requirement for infant delivery prior to 34 weeks, but rather reported on preeclampsia in general, often irrespective of the timing of the onset of preeclampsia or the presence of pre-term delivery of the infant. The proportion of overall preeclampsia events associated with aPL was between 11% and 29% according to 4 case-control studies.<sup>22</sup> An estimated approximately 10%-20% of pre-term deliveries due to preeclampsia are attributable to APS.

Multiplying the incidence of pre-term deliveries due to preeclampsia (4 per 100 000 person-years in the general population) by the proportion attributable to APS (10%-20%), the estimated incidence of APS manifesting as pre-term deliveries due to preeclampsia is approximately 0.4-0.8 per 100 000 person-years.

#### Incidence of Antiphospholipid Syndrome Overall

Table 2 lists the ranges of estimates of incidence of APS from this study and the minimum and maximum estimates from the 2 aforementioned studies.<sup>4,7</sup>

Adding together the ranges of estimates for the most common manifestations of thrombotic APS, the estimated incidence of thrombotic APS is approximately 5.3-10.8 per 100 000 person-years in the general population. This is compared to the minimum estimate of 1.8<sup>7</sup> and the maximum estimate of 65<sup>4</sup> identified in the published literature. Adding together the ranges of estimates for the criteria manifestations of obstetric APS, the estimated incidence of obstetric APS is approximately 1.8-2.9 per 100 000 person-years in the general population. This is compared to the minimum estimate of 0.2<sup>7</sup> and the maximum estimate of 15<sup>4</sup> identified in the published literature. Combining the ranges of estimates for thrombotic and obstetric APS, the estimated incidence for APS overall is approximately 7.1-13.7 per 100 000 person-years in the general population. This is compared to the minimum estimate of 2<sup>7</sup> and the maximum estimate of 80<sup>4</sup> identified in the published literature.

## Discussion

The incidence of APS is uncertain due to an inadequate number of studies rigorously analyzing aPL profiles that enable confirmation of persistency and fulfillment of current APS classification criteria. With these caveats in mind, a targeted review of the literature and applied methodology were performed to derive a best available estimate for the incidence of APS, which was found to be approximately 7.1-13.7 per 100 000 person-years in the general population of the USA. The range of estimated incidence lies near the geometric mean of the minimum estimate of 2 per 100 000 person-years<sup>7</sup> and the maximum estimate of 80 per 100 000 person-years<sup>4</sup> within the existing literature. Some expert authors previously estimated the incidence of APS to be approximately 5 cases per 100 000 person-years based upon personal interpretation of the published data and clinical experience, but no methodology or explanation was given for this estimate.<sup>25</sup>

Although published only in meeting abstract form to date, 2 additional studies on the

incidence of APS have been reported. Using electronic medical records from a tertiary university hospital in Argentina, 1 study reported an overall incidence of 2.6 (95% CI 1.9-3.2) per 100 000 person-years.<sup>26</sup> Another study from Brescia, Italy, reviewed medical records and estimated the incidence of primary APS among persons 18 to 50 years old to be 3.7 (95% CI 1.7-7.1) per 100 000 person-years.<sup>27</sup> Details of the methodologies are limited by the meeting abstract format, but it appears likely that these studies had many of the same limitations as the study from the USA—most importantly, reliance on clinical evaluation and diagnosis of APS. In a Letter to the Editor, authors reported an incidence of 1.1 per 100 000 person-years according to data from the Rare Disease Registry of Piedmont and Aosta Valley, Italy.<sup>28</sup> In addition to reliance on clinical evaluation and diagnosis of APS, this study may have been limited by incomplete reporting to the registry.<sup>29</sup>

Incomplete evaluation for APS is likely common in clinical practice. For example, aPLs are frequently not tested following VTE; in fact, the American College of Chest Physicians guidelines do not include APS among the criteria to determine the duration of anticoagulation following VTE.<sup>30</sup> As noted, such practices result in lower estimates of the incidence of APS compared to the true incidence, as observed in the study from Olmstead County, USA,<sup>7</sup> and presumably other studies.<sup>26-28</sup>

Although APS is known to occur in children,<sup>31</sup> no estimates of the incidence of APS in children have been published,<sup>32</sup> and this may influence estimates of the incidence of APS overall. For example, in the aforementioned study conducted in Olmsted County,<sup>7</sup> the authors reported an incidence of 2.1 per 100 000 person-years among adults aged  $\geq 18$  years. Based on population figures published in the manuscript and assuming no cases of APS were identified in children, the incidence among all persons would be approximately 1.6 per 100 000 person-years. This is a considerable relative decrease in the estimated incidence rate, but

compared to the wide range of incidence estimates reported in this current study, the overall impact of including versus excluding children is small. Because the age of patients was frequently not reported in the studies identified for this current study's estimation, a general population incidence estimate that included persons of all ages was determined.

In addition to the limitations of the published literature, the clinical diagnosis of APS, and the current APS classification criteria,<sup>33</sup> this current study's methodology had limitations of its own. Importantly, it was assumed that the proportion of persons with aPL without true APS was similar between persons with and without thrombotic or obstetric events (i.e., the proportion of persons with asymptomatic or transient aPL in the general public was subtracted from the estimates of persons with thrombotic or obstetric events and aPL). This method assumed that no instances of MI or stroke that occurred in older patients were attributable to APS; this is unlikely to be true and may have led to an underestimate of the true incidence of APS. Transient ischemic attacks were not included in the assessment of stroke because they were not included in the best available estimates of the presence of aPL. Because transient ischemic attacks often precede strokes, this was an additional reason for not including transient ischemic attacks in the assessment of stroke (i.e., to avoid both transient ischemic attack and stroke being counted in the same person). Because thrombotic and obstetric events in APS may recur, some prevalent APS events (recurrent events) may have been categorized as incident events, and this would have overestimated the number of incident events. Although patients with obstetric APS may also have thrombotic manifestations of APS, this appears to occur in less than 10% of women<sup>2,34,35</sup> and is unlikely to have substantially affected the accuracy of the incidence estimates. In general, some of the included studies were not population-based or had other methodological limitations; the potential effects on our incidence estimate are difficult to quantify. Finally, the targeted literature review was neither systematic nor exhaustive. The attempt to identify the best available estimates may have inadvertently omitted important published results. However, given the current challenges in assessing the incidence of APS, it appears unlikely that any omitted studies would have substantially improved the overall precision of the estimates.

In summary, the true incidence of APS remains unclear because of diverse aPL-related clinical

**Table 2.** Estimated Incidence of APS Compared to Other Published Estimates in the USA

	Minimum Estimate <sup>7</sup>	This Study	Maximum Estimate <sup>4</sup>
Incidence of thrombotic APS per 100 000 person-years	1.8	5.3-10.8	65
Incidence of obstetric APS per 100 000 person-years	0.2	1.8-2.9	15
Incidence of APS overall per 100 000 person-years	2.1	7.1-13.7	80

APS, antiphospholipid syndrome.

manifestations, inconsistent definitions of aPL positivity, under-recognition of the disease, and limited population-based studies. Using a targeted literature review and applied methodology, this study estimated an incidence of APS of 7.1-13.7 per 100 000 person-years and likely represents a more accurate estimate than previously published estimates. Overall, an improved estimation was possible using this approach, but large, contemporary, population-based studies that reasonably adhere to the APS classification criteria are needed to further refine estimates of the incidence of APS.

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