The adjusted Global AntiphosPholipid Syndrome Score (aGAPSS) for risk stratification in young APS patients with acute myocardial infarction

The adjusted Global AntiphosPholipid Syndrome Score (aGAPSS) for risk stratification in young APS patients with Acute Myocardial Infarction

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Abstract

Background: Young adults with acute myocardial infarction are a critical group to examine for the purpose of risk factor stratification and modification. In this study we aimed to assess the clinical utility of the adjusted Global AntiphosPholipid Syndrome Score (aGAPSS) for the risk stratification of acute myocardial infarction in a cohort of young patients with antiphospholipid syndrome (APS).

Methods: The analysis included 83 consecutive APS patients (≤ 50 years old) who presented with arterial or venous thromboembolic events. Data on cardiovascular risk factors and antiphospholipid antibodies (aPL) positivity were retrospectively collected. The aGAPSS was calculated by adding the points corresponding to the risk factors, based on a linear transformation derived from the ß regression coefficient as follows: 3 for hyperlipidaemia, 1 for arterial hypertension, 5 for aCL IgG/IgM, 4 for anti-b2 glycoprotein I IgG/IgM and 4 for LA.

Results: Higher aGAPSS values were observed in patients with acute myocardial infarction when compared to the others [mean aGAPSS 11.9 (S.D. 4.15, range 4-18) Vs. (mean aGAPSS 9.2, S.D. 5.1, range 1-17); T test:$p<0.05$]. Significantly higher aGAPSS values were also seen in patients with acute coronary syndrome compared to patients with a history of peripheral or cerebrovascular arterial thrombotic events [mean aGAPSS 11.9 (S.D. 4.15, range 4-18) Vs. (mean aGAPSS 6.7, S.D. 5.7, range 1-17); T test: $P<0.005$].

Conclusions:

The aGAPSS is based upon a quantitative score and could aid risk stratifying APS patients younger than 50 years for the likelihood of developing coronary thrombotic events and may guide pharmacological treatment for high-risk patients.

1.1 Introduction

Acute myocardial infarction amongst young patients (for the purpose of this work 'young' refers to adults younger than 50 years old) is an uncommon event. However, it might represent a life threating situation being associated with a significantly increased mortality and morbidity[1,2]. Epidemiological studies have demonstrated that younger adults who develop acute coronary syndrome have an increased prevalence of cardiovascular risk factors, including male gender, smoking, family history of cardiovascular events and [1–3].Conversely, these patients present a lower prevalence of hypertension and diabetes[2,3]. Angiography is more likely to show a reduced coronary atherosclerosis when compared with older patients with cardiovascular events [2]. In the setting of underlying systemic autoimmune diseases, premature cardiovascular disease (CVD) deserves even more attention as conditions such as systemic lupus erythematosus (SLE) or rheumatoid arthritis (RA) have been associated with the development of premature CVD [4]. The latter has even been implemented in the national institute of health and care excellence (NICE) screening questions to risk stratify patients for the development of CVD[5].

Young adults are a critical group to examine for the purpose of risk factor stratification and modification. In this particular patient group, a thorough history for conventional risk factors including a family history for inherited thrombophilias and often also investigations for any underlying acquired

thrombophilia should be warranted as positive results might have an impact on the therapeutic choices [6].

The most common acquired thrombophilia is antiphospholipid syndrome (APS), an autoimmune disorder characterized by arterial and venous thrombosis and/or pregnancy morbidity in the presence of persistent positivity for aPL[7]. The current classification criteria for APS include three laboratory tests: lupus anticoagulant (LA), anticardiolipin (aCL) and anti-β2 glycoprotein-I (β2GPI). To prevent the detection of transient antibodies, tests must be positive on more than 2 occasions, at least 12 weeks apart[7].

To date, identifying patients with aPL who are at higher risk for developing any thrombotic event is still an unmet clinical need and remains a major challenge for the treating physician. Recently, our group conceived a risk score for clinical manifestations of APS [the global APS score (GAPSS)] that takes into account the combination of independent cardiovascular risk factors and the aPL positivity profile [8]. The aim of our study was to assess the clinical utility of the adjusted GAPSS (aGAPSS) score for risk stratification of acute myocardial infarction occurrence in a cohort of young patients with thrombotic events.

2.1 Patients and methods:

2.2 Patients

This retrospective study included 83 consecutive APS patients who attended the Giovanni Bosco Hospital, Turin, Italy and the Louise Coote Lupus Unit at St

Thomas' Hospital, London, UK. Inclusion criteria included: a) history of thrombotic APS (venous and/or arterial) and b) age ≤ 50 years old at the time of the first event. Patients with myocardial infarction aged ≤ 50 years old are routinely checked for aPL in both centres as part of the good clinical practice. When found positive, aPL testing was repeated at least 12 weeks apart. The patients included in the analysis had a persistent aPL positivity and fulfilled the Sydney criteria for APS [7].Fifty-three patients had at least one episode of arterial thrombosis (60%), 44 (50%) had at least one episode of venous thrombosis. Thirteen patients (15%) had a history of acute myocardial infarction. The diagnosis of acute myocardial infarction was based on typical chest pain at rest lasting for >20 min and/or electrocardiogram changes and dynamic changes in troponin levels according to international standards [9]. A diagnosis of acute coronary syndrome was confirmed by percutaneous coronary intervention. Demographic, clinical and laboratory characteristics are summarized in Table 1.

2.3 Cardiovascular risk factors assessment

Cardiovascular risk factors (including hypertension, dyslipidaemia, diabetes, hormone replacement therapy and smoking) were assessed following the National Institute for Health and Care Excellence (NICE) guidelines [5]. In detail, enrolled patients underwent a physical examination, blood pressure determination and phlebotomy for vascular risk factors. Arterial hypertension

was defined as an appropriately sized cut-off (140/90 mmHg or higher) [5], high blood pressure on at least two occasions or use of oral antihypertensive medications. Serum total and high-density lipoprotein (HDL) cholesterol levels were determined with standardized enzymic methods and interpreted according to current cut-off values [5]. For patients with acute myocardial infarction, underlying atrial fibrillation was ruled out in with 24h Holter monitoring.

2.4 Autoantibody detection

The aPL profile included aCL, LA and anti-ß2 glycoprotein I (anti-ß2GPI) antibodies. The aCL and anti-ß2GPI were detected by ELISA as described previously [10,11]. Plasma samples were tested for the presence of LA according to the recommended criteria from the International Society on Thrombosis and Haemostasis (ISTH) Subcommittee on Lupus Anticoagulant/Phospholipid-Dependent Antibodies [12][13].

2.5 Adjusted GAPSS calculation

The cumulative aGAPSS was calculated for each patient as previously reported by adding together all points corresponding to the risk factors [14].

In brief, the GAPSS was developed and validated in 211 consecutive SLE patients who were randomly divided into two sets by a computer-generated randomized list. Data on clinical disease manifestations, conventional cardiovascular risk

factors, aPL profile, antinuclear antibodies (ANA), extractable nuclear antibodies (ENA)and antibodies against double stranded DNA (anti-dsDNA) were collected and included in the analysis. We developed the GAPSS in the first set of patients (n = 106), assigning the risk factors identified by multivariate analysis and weighted points proportional to the ß regression coefficient values. Assigned points to risk factors based on this linear transformation of the corresponding ß regression coefficient were 3 for hyperlipidaemia, 1 for arterial hypertension, 5 for aCL IgG/IgM, 4 for anti-b2GPI IgG/IgM, 3 for aPS-PT IgG/IgM and 4 for LA. The GAPSS was then validated in a second set of patients with SLE (n = 105)[8]and in a third set of patients with primary APS (n = 62)[15]. The GAPSS was further applied and validated by two independent groups [16][17].In order to increases the generalizability of the findings, a complementary analysis was applied in this cohort of patients by using an adjusted version of the score. This included only aPL testing included in the current classification criteria for APS (excluding aPS-PT, not routinely available in all the laboratories). Data are presented as adjusted GAPSS (aGAPSS). For the purpose of this study, all computed variables refer to values/parameters assessed within one year from the occurrence of the thrombotic event.

2.6 Statistical analysis

Categorical variables are presented as number (%) and continuous variables are presented as mean (S.D.). The significance of baseline differences was

determined by the chi-squared test, Fisher's exact test or the unpaired t-test, as appropriate. A two-sided P-value <0.05 was statistically significant. All statistical analyses were performed using SPSS version 19.0 (IBM, Armonk, NY, USA).

3.1 Results:

A total of 83 consecutive APS patients (age ≤50 years old at the time of the first event, mean 44,6 (SD 11,3), female 90%) with a history of previous thrombotic events (60% arterial and 50% venous) were included in the analysis. Thirty-one patients fulfilled the current classification criteria for primary APS (PAPS), while in the remaining 52 patients APS was associated with SLE (secondary APS; SAPS). Thirteen patients (15%) had a history of acute myocardial infarction. Of note, 6 of those 13 patients (46%) had also an history of ischemic stroke. Among patients with a history of myocardial infarction, no statistical difference (in terms of age, sex, aPL profile, cardiovascular risk factors, treatments, previous history of thrombotic events) was found between PAPS and SAPS. Patients with acute coronary syndrome presented a mean aGAPSS of 11.9 (S.D. 4.15, range 4-18). Significantly higher aGAPSS values were seen in patients with acute myocardial infarction when compared with those with history of any other thrombotic events [mean aGAPSS 11.9 (S.D. 4.15, range 4-18) Vs. (mean aGAPSS 9.2, S.D. 5.1, range 1-17); T test p:<0.05].Significantly higher aGAPSS values were also seen when comparing patients with acute coronary syndrome with patients with a history of peripheral or cerebrovascular arterial thrombotic events [mean

aGAPSS 11.9 (S.D. 4.15, range 4-18) Vs. (mean aGAPSS 6.7, S.D. 5.7, range 1-17); T test: p <0.005]. When separating for cardiovascular risk factors, hypercholesterolemia was significantly higher in the group that developed myocardial infarction compared with patients with a history of any thrombosis and patients with history of arterial thrombotic events (Chi square test: p< 0.0001 and p< 0.0001). Furthermore, when evaluating the aPL positivity profiles in the different cohorts, we found significantly higher rate of multiple positivity (more than one aPL) for LA, aCL (IgG/IgM), anti-ß2GPI antibodies (IgG/IgM) in the group that developed myocardial infarction compared with patients with a history of any other arterial thrombotic event alone (Chi square test: p<0.05 for all aPL). However, when focusing on the *so-called* triple positivity, we failed to observed any statistical difference when comparing patients with acute myocardial infarction with those with other thrombotic manifestations (Table 2).

No statistical significant differences were observed when comparing separately each cardiovascular risk factor (smoking, diabetes, arterial hypertension) nor other thrombotic risk factor (hormonal therapy, immobilization, surgery, malignancy).

4.1 Discussion:

In this study we demonstrate the clinical relevance of the aGAPSS for risk stratification in young patients with acute myocardial infarction. Our cohort

comprehended 83 young patients (≤ 50 years old) who had experienced at least one thrombotic events (arterial and/or venous).

Our group recently published a comprehensive series of studies developing and validating the global APS score (GAPSS) in different patients populations[8]. The GAPSS model was developed in patients with SLE and higher GAPSS scores were observed in patients who experienced thrombosis and/or pregnancy loss compared with those without clinical events. Moreover, the GAPSS score was evaluated in a subsequent prospective study of 51 SLE patients10 and in 62 consecutive patients with primary APS[18]. The GAPSS model was further applied and validated by two independent groups, confirming that higher GAPSS values were seen in patients who had clinical APS manifestations (such as thrombosis or pregnancy complications) compared to patients without APS manifestations[16][17]. In the original GAPSS, anti-phosphatidylserine/prothrombin antibodies (aPS-PT) were included in the score. However, these are not currently part of the international consensus classification criteria [7]. Moreover, aPS-PT antibodies are not routinely tested in most clinical laboratories, and the inclusion as part of the score might be of concern to many. To address this concern, in our current study we applied the adjusted GAPSS(excluding aPS-PT) demonstrating its clinical utility for the stratification of patients for their rate of thromboembolic events [14].

Furthermore, we showed that higher aGAPSS values are seen in patients who experienced acute myocardial infarction when compared to those with

thrombosis alone. In addition, when stratifying the patients and analyzing those patients who developed at least one arterial thromboembolic event, the aGAPSS was significantly higher in patients who experienced acute myocardial infarction. When comparing patients with PAPS and SAPS who suffered from myocardial infarction, no differences were observed in demographic, clinical or laboratory characteristics. It has been shown that in young patients who develop acute coronary syndrome, despite having a high rate of cardiovascular risk factors, angiographic data indicate a less prominent atherosclerosis compared to general population [1-3]. Our results are in line with these findings, showing an increased proportion of patients with hyperlipidemia in the patients who developed acute coronary syndrome, despite the fact that there were no significant differences between groups with regards to the presence of arterial hypertension. Thus, there is growing interest and necessity of thrombophilia screening and aPL testing in young patients who develop myocardial infarction. Besides, one should consider that it was not among the scopes of this study to assess the prevalence of aPL in a cohort of young patients with myocardial infarction. Our analysis supports the idea that a combination of aPL tests should be warranted when assessing the risk of acute coronary syndrome in young patients. Furthermore, in these patients, the aGAPSS might represents a substantial tool in quantifying the risk for acute myocardial infarction, potentially impacting on therapeutic long-term choices and options. Indeed, while anti-platelets agents are the gold standard therapies in acute coronary

syndrome in the general population, there is still a debated whether APS patients with arterial thrombosis should undergo long-term anticoagulation (and more critically, the intensity of such anticoagulation) as best treatment option. This aspect is currently highly debated and it was matter of discussion during the 14th International Congress on aPL Task Force [19–23] and in the more recent 15th International Congress on aPL Task Force [24]. The prevalence of aPL in the general population is estimated to be between 1 and 5 % [25]. Multiple studies have investigated the association of aPL and acute myocardial infarction [26][27][28][29][30][31][32][33](Table 3). Among other, recently Andreoli and colleagues found an estimated frequency of 11% in patients with myocardial infarction in aPL positive patients [34]. However, the true incidence of APS among survivors of acute coronary syndrome is difficult to estimate in such a rare condition.

We acknowledge few limitations for our study. Firstly, the use of a cross-sectional approach generally provides only a 'snapshot' and it may therefore be possible that individual scores would give a different aGAPSS when conducted at a different point of time. A future prospective validation of our findings in the specific setting of acute coronary syndrome is highly needed. However, one should acknowledge that APS is a rare condition and acute coronary syndrome represents about 5%[35] of the clinical presentation of this condition. While a longitudinal study would be very informative to confirm our findings, a

prospective data collection may be challenging and would requires international joint efforts. From that perspective, it is worth mentioning the AntiPhospholipid syndrome alliance for clinical trials and International networking (APS ACTION) is the first-ever international research network that has been created specifically to design and conduct well-designed, large-scale, multicenter clinical studies in persistently aPL-positive patients [34,36–38].

Finally, the effect of therapy and therapy compliance, a significant variable when evaluating risk, could not be assessed, as treatment was not controlled in this cohort, but varied according to the clinical manifestations and the clinician's judgement.

In the future, with prospective studies confirming our findings, aGAPSS might be a valid tool for the risk quantification of acute myocardial infarction in young patients ≤ 50 years old. The aGAPSS is based upon a quantitative score and will aid risk stratifying patients < 50 years for the likelihood of developing coronary thrombotic events and may consequently guide pharmacological treatment for high-risk patients.

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Legend of Tables and Figures:

Table 1. *Demographic, clinical and laboratory characteristics of the cohort*

Table 2. *Patients cardiovascular risk factors and aPL positivity between groups*

Table 3*. Studies investigating the association of aPL and acute myocardial infarction in patients aged <55 years' old*