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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. 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, and family history of cardiovascular events [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

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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 antiphospholipid antibodies (aPL) [7]. The current classification criteria for APS include three laboratory tests: lupus anticoagulant (LA), anticardiolipin (aCL) and anti-β2 glycoprotein-I (β2GPI) antibodies. To prevent the detection of transient antibodies, tests must be positive on >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 APS patients with thrombotic events.

2. Patients and methods

2.1. 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.

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

Patients characteristics	All ($n = 83$)	%
Female sex	75	90
Age, mean (S.D.), years	44,6 (11,3)	
Disease duration, mean (S.D.), years	11,4 (7,8)	
Caucasians, n	82	99
Arterial thrombosis, n	53	64
Venous thrombosis, n	44	53
Acute myocardial infarction	13	16
PAPS, n	35	42
SLE and APS, n	48	58
Arterial hypertension, n	27	33
Hyperlipidemia, n	16	19
LA, n	38	46
aCL IgG/M, n	65	78
IgG	60	72
IgM	35	42
Anti-Beta2GPI IgG/IgM, n	44	53
IgG	39	47
IgM	12	15
Triple aPL positivite	27	33

2.2. 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 mm Hg 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 enzymatic methods and interpreted according to current cut-off values [5]. For patients with acute myocardial infarction, underlying atrial fibrillation was ruled out in with 24 h Holter monitoring.

2.3. Autoantibody detection

The aPL profile included aCL, LA and 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].

2.4. 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 β-regression coefficient values. Assigned points to risk factors based on this linear transformation of the corresponding β-regression coefficient were 3 for hyperlipidaemia, 1 for arterial hypertension, 5 for aCL IgG/IgM, 4 for anti-ß2GPI 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 increase 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.

2.5. Statistical analysis

Categorical variables are presented as numbers (%) 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).

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