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Published:

- with international search report (Art. 21(3))
- with sequence listing part of description (Rule 5.2(a))

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2 May 2013

(54) **Title:** METHODS FOR PREDICTING RISK OF STROKE

(57) **Abstract:** Methods of determining risk for stroke in a patient, as well as methods of determining a subject's need for anti-coagulation therapy are disclosed. The method comprises measuring a level of derivatives of reactive oxygen metabolites (DROMs) in a biological sample obtained from the subject, wherein an increased level of DROMs, relative to a control level, is indicative of the subject's need for anticoagulation therapy. Further provided are methods of decreasing risk of stroke in a subject, methods of determining the efficacy of a therapeutic agent, and methods of monitoring a subject's risk of stroke.



INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 11/45903

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61B 5/145; C12Q 1/00; G01N 33/48 (2011.01)

USPC - 600/301; 435/4

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC(8) - A61B 5/145; C12Q 1/00; G01N 33/48 (2011.01)

USPC - 600/301; 435/4

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC - 435/25, 435/28; 600/300 (keywords below)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

USPTO PubWest (PGPB,USPT,USOC,EPAB,JPAB), Google Scholar: Dudley, Negi, cha2ds2-vasc, CHADS2, ROS, ROM, DROM, superoxide, peroxide, oxygen, radical, reactive, low, fibrillation, flutter, atrial, anti-coagulant, anti-clotting, thinning, thinner, stroke, warfarin, coumarin, aspirin, measure, detect, determine, assess, assay, evaluate

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	PAMUKCU, et al. Simplifying stroke risk stratification in atrial fibrillation patients: implications of the Cha.sub.2DS.sub.2VASc risk stratification scores. Age and Ageing ePub 26 May 2010, 39:533-535; pg. 533, col 1, para 1; pg. 533, col 2, para 1; pg. 534, col 1, para 3-col 2, para 1; pg. 535, col 1, para 1	1-9, 31-32
Y	US 2008/0033258 A1 (DUDLEY, et al.) 7 February 2008 (07.02.2008) abstract; para [0019]; [0026]; [0030]	1-9, 31-32
Y	Puwanant, et al. Role of the CHADS2 score in the evaluation of thromboembolic risk in patients with atrial fibrillation undergoing transesophageal echocardiography before pulmonary vein isolation. J Am Coll Cardiol. 2009, 54(22):2032-2039; pg 20320	1-9, 31-32
A	US 2007/0218457 A1 (MCKIM) 20 September 2007 (20.09.2007)	1-9, 31-32
A	US 2009/0325163 A1 (HELGADOTTIR, et al.) 31 December 2009 (31.12.2009)	1-9, 31-32

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 11/45903

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☒ Claims Nos.: 10-17, 21, 22, 26-30, 33, 37, 39-41, 47, and 48
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1.

Group I: claims 1-9 and 31-32, drawn to a method of determining a subject's need for anti-coagulation therapy, wherein the subject has a known CHADS2 or CHA2DS2-VASc score which is less than 2, comprising the step of measuring a level of derivatives of reactive oxygen metabolites (DROMs) in a biological sample obtained from the subject, wherein an increased level of DROMs, relative to a control level, is indicative of the subject's need for anti-coagulation therapy.

- Please see extra sheet for continuation -

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: 1-9, 31 and 32

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 11/45903

Continuation of Box III: Lack of Unity of Invention

Group II: claims 18-20, drawn to a method of decreasing risk of stroke in a subject, by (i) identifying the subject as a subject with a low to intermediate level of risk for stroke, (ii) identifying the subject as a subject with an increased level of DROMs relative to a control level, and (iii) administering an effective amount of an anti-coagulant to the subject.

Group III, claims 23-25, drawn to a method of determining a subject's need for anti-coagulation therapy, by measuring a level of DROMs and a level of C-reactive protein (hs-CRP), in a biological sample obtained from the subject

Group IV: claims 34-36, 42-46, drawn to a method of determining the efficacy of a therapeutic agent, by (i) administering to a subject a therapeutic agent and (ii) measuring a level of hs-CRP, DROMs, or both, in a biological sample obtained from the subject.

The inventions listed as Groups I-IV do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

The inventions of Groups I-III do not include the inventive concept of a method of determining the efficacy of a therapeutic agent by (i) administering to a subject a therapeutic agent and (ii) measuring a level of C-reactive protein (hs-CRP), DROMs, or both, in a biological sample obtained from the subject, as required by Group IV.

The inventions of Groups I and III do not include the inventive concept of a method of decreasing risk of stroke in a subject by (i) identifying the subject as a subject with a low to intermediate level of risk for stroke, (ii) identifying the subject as a subject with an increased level of DROMs relative to a control level, and (iii) administering an effective amount of an anti-coagulant to the subject, if the CHADS2 or CHA2DS2-VASc score is 2 or higher, or if the CHADS2 or CHA2DS2-VASc score is less than 2 and the level of DROMs is increased relative to a control level, as required by Group II.

The inventions of Groups I-III share the technical feature of a method of claim 1. However, this shared technical feature does not represent a contribution over prior art as being obvious over US 2009/0325163 A1 to Helgadottir et al. (hereinafter "Helgadottir") in view of US 2008/0033258 A1 to Dudley et al. (hereinafter "Dudley") as follows:

Helgadottir teaches a method of determining a subject's need for anti-coagulation therapy (para [0043]-[0044]), comprising the step of measuring a level of a biomarker in a biological sample obtained from the subject (para [0025] and [0041]), wherein an increased level of the biomarker, relative to a control level, is indicative of the subject's need for anti-coagulation therapy (para [0041]-[0044]). Helgadottir does not specifically teach the subject has a known CHADS2 or CHA2DS2-VASc score which is less than 2, or the biomarker is a DROM. However, Helgadottir does teach the CHADS2 score is the best validated method of determining risk of stroke (para [0015]), treatment of subjects having a CHADS score of 2 or more with an anticoagulant (para [0015]), and measuring a level of various biomarkers of risk of atrial fibrillation and stroke to determine if anticoagulant treatment is appropriate (para [0041] and [0043]-[0044]).

Dudley teaches a method of measuring a level of biomarkers of risk of atrial fibrillation, comprising measuring a level of DROMs (abstract). It would have been obvious to one of ordinary skill in the art to have performed a method of determining a subject's need for anti-coagulation therapy as claimed, wherein the subject has a known CHADS2 of less than 2, and the biomarker is a DROM, in view of Helgadottir teaching measurement of multiple biomarkers indicative of risk of atrial fibrillation and stroke to determine if anticoagulant treatment is appropriate (para [0041]), and in light of Dudley teaching measurement of DROMs as an indicator of atrial fibrillation (abstract), wherein atrial fibrillation accounts for 15-20% of strokes (Dudley, para [0004]), since a skilled artisan at the time would have readily appreciated use of DROMs as an indicator of atrial fibrillation and strokes in the method taught by Helgadottir, for more accurate risk assessment and therapeutic determination of strokes by use of multiple known risk factors of atrial fibrillation and strokes in patients with known CHADS2 scores below 2. As said method would have been obvious to one of ordinary skill in the art at the time of the invention, this cannot be considered a special technical feature that would otherwise unify the groups.

The inventions of Groups III-IV share the technical feature of a method of determining a subject's need for anti-coagulation therapy, comprising the steps of measuring a level of DROMs and a level of hs-CRP, wherein an increased level of DROMs and an increased level of hs-CRP, relative to a control level, is indicative of the subject's need for anti-coagulation therapy. However, this shared technical feature does not represent a contribution over prior art as being obvious as follows:

Helgadottir teaches a method of determining a subject's need for anti-coagulation therapy (para [0043]-[0044]), comprising the steps of measuring a level of a biomarker and measuring a level of hs-CRP in a biological sample obtained from the subject (para [0025] and [0041]), wherein an increased level of a marker and an increased level of hs-CRP, relative to a control level, is indicative of the subject's need for anti-coagulation therapy (para [0041]-[0044]).

Helgadottir does not specifically teach the biomarker is DROMs. However, Helgadottir does teach measuring a level of various biomarkers of risk of atrial fibrillation and stroke (para [0041]). Dudley teaches a method of measuring a level of biomarkers of risk of atrial fibrillation, comprising measuring a level of derivatives of DROMs (abstract). It would have been obvious to one of ordinary skill in the art to combine Helgadottir and Dudley by performing a method of determining a subject's need for anti-coagulation therapy, wherein the biomarker is hs-CRP, as in Helgadottir and DROMs as in Dudley, because Helgadottir teaches measurement of multiple biomarkers indicative of risk of atrial fibrillation and stroke (para [0041]), and Dudley teaches measurement of DROMs as an indicator of atrial fibrillation (abstract), wherein atrial fibrillation accounts for 15-20% of strokes in the US (para [0004]), to improve accuracy of risk assessment and therapeutic determination of strokes by use of multiple known risk factors of atrial fibrillation and strokes.

Groups I-IV therefore lack unity under PCT Rule 13 because they do not share a same or corresponding special technical feature.