

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
15 December 2011 (15.12.2011)

(10) International Publication Number
WO 2011/156587 A2

(51) International Patent Classification:
G06F 19/00 (2011.01)

(21) International Application Number:
PCT/US2011/039788

(22) International Filing Date:
9 June 2011 (09.06.2011)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/353,196 9 June 2010 (09.06.2010) US

(71) Applicant (for all designated States except US): **DAI-
ICHI SANKYO, INC.** [US/US]; Two Hilton Court, Par-
sipppany, New Jersey 07054 (US).

(72) Inventors; and

(71) Applicants : **CASCIANO, Julian** [US/US]; 2 Silver
Springs Court, Katonah, New York 10536 (US). **FOX,
Eben, S.** [US/US]; 909 Carleton Road, Westfield, New
Jersey 07090 (US).

(74) Agents: **LEE, Wan, Chieh** et al.; King & Spalding LLP,
1185 Avenue of the Americas, New York, New York
10036 (US).

(81) Designated States (unless otherwise indicated, for every
kind of national protection available): AE, AG, AL, AM,
AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ,
CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO,
DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT,
HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP,
KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD,
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SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR,
TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every
kind of regional protection available): ARIPO (BW, GH,
GM, KE, LR, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG,
ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ,
TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK,
EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU,
LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK,
SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ,
GW, ML, MR, NE, SN, TD, TG).

Published:

— without international search report and to be republished
upon receipt of that report (Rule 48.2(g))

(54) Title: METHODS AND SYSTEMS FOR ANTICOAGULATION RISK-BENEFIT EVALUATIONS

(57) Abstract: Methods for identifying an optimal treatment option from a plurality of treatment options, wherein said optimal treatment option provides the largest net benefit (i.e., differential between benefits and risks) for a patient. The methods may compare the benefit of reduced ischemic or stroke events to the bleeding risks associated with anticoagulant treatment before recommending and/or selecting a treatment option that provides the largest net benefit for administration to the patient. Specifically, the methods may evaluate the impact of a particular treatment recommendation by weighing the benefit of an anticoagulant treatment with bleed risks.



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METHODS AND SYSTEMS FOR ANTICOAGULATION RISK-BENEFIT EVALUATIONS

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority benefit, under 35 U.S.C. § 119(e), of U.S. Provisional Patent Application No. 61/353,196, filed June 9, 2010, the contents of which application are hereby incorporated by reference in their entirety.

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FIELD OF INVENTION

[0003] The present invention relates generally to treatment of patients in atrial fibrillation. More specifically, the invention relates to methods for treating patients in atrial fibrillation with an oral anticoagulant administered at a regiment determined based on each individual patient's stroke and bleed risk factors.

BACKGROUND OF THE INVENTION

[0004] The decision to give anticoagulants to patients with non-valvular atrial fibrillation (AF) is often complex, requiring physicians to balance genuine safety concerns with disease risk. According to the Fuster et al., ACC/AHA/ESC Practice Guidelines, JACC Vol. 48, No. 4, August 15 e149-246 (2006), "[a]ntithrombotic therapy to prevent thromboembolism is recommended for all patients with AF, except those with lone AF or contraindications." However, the decision to utilize the most effective treatment (vitamin K antagonist) is only recommended in patients with multiple "moderate" risk factors for ischemic stroke. The threshold, at which AF patients benefit from warfarin varies, is not simply based on ischemic risk (the focus of the guidelines), but must also be balanced against bleeding risk. The recommendation of the guidelines is to treat all patients with warfarin who are at "high" risk for ischemic stroke, but only selectively with "moderate" risk. While

unquantified, the “selective” treatment recommendation is used because patients have a varying bleeding risk profile. If warfarin carried no bleeding risk (or that equal to aspirin), there would not be a need to stratify patient ischemic risk; instead, warfarin would be recommended for everyone with AF. However, since warfarin does carry significant bleeding risk, the guidelines focus on classifying ischemic risk. The guidelines promulgate the use of an ischemic risk predictive rule in an effort to manage this amorphous bleeding risk.

[0005] One exemplary model for predicting ischemic risk is the CHADS₂ predictive rule, described in O’Brien et al., “Costs and Effectiveness of Ximelagatran for Stroke Prophylaxis in Chronic Atrial Fibrillation,” JAMA, Vol. 293, No. 6, 699-706 (2005). O’Brien adjusts ischemic stroke risk in this model based on the presence of covariates in the CHADS₂ risk scheme. However, this approach to the determination of hemorrhagic risk lacks symmetry, as the model universally applies uniform bleeding risk rates.

[0006] Making oral anti-coagulant treatment decisions in atrial fibrillation at either end of the risk spectrum (i.e. High Stroke & Low Bleed Risk or Low Stroke & High Bleed Risk) is relatively straight forward. However, treatment decisions inside these extremes are more complex and require careful consideration. It is important to emphasize risk-based treatment decisions where bleeding risk is weighed against clot risk to define patient groups with corresponding risk/benefit ratios to guide treatment. It is therefore an object of the invention to provide methods for treating patients in atrial fibrillation with an oral anticoagulant administered at an appropriate regiment determined based on variable stroke and bleed risks for each patient.

SUMMARY OF THE INVENTION

[0007] In accordance with the foregoing objectives and others, the present invention provides a method for reducing a patient’s risk of bleed under anticoagulant treatment. The method comprises a step for determining a cumulative net benefit for each of two or more treatment options using a Markov chain simulation for predicting a cumulative period of life extension and the occurrence of stroke and bleed events during the cumulative period of life extension under a selected treatment option for a cohort of patients. The simulation comprises generating a risk profile for the patient based on the patient’s medical history. The risk profile comprises a health state comprising an event condition of the patient and a course

of treatment based on the event condition. The event condition is selected from a group consisting of lack of stroke or bleed events, recurrent and non-recurrent stroke events, recurrent and non-recurrent bleed events, and combinations of stroke events and bleed events. The course of treatment is selected from the group consisting of: (i) administration of said treatment option at one or more different dosages, (ii) temporary discontinuation of said treatment option, and (iii) permanent discontinuation of said treatment option. In addition, a numerical value of net benefit is associated with the health state. The numerical value corresponds to a period of life extension in the health state predicted by the simulation, reduced by an amount corresponding to the patient's reduction in quality of life arising from the event condition or the course of treatment for the selected treatment option. The simulation further comprises assigning a probability for the occurrence of each predicted stroke event under each treatment option by attributing weighted values to two or more stroke risk factors from said patient's medical history, and a probability for the occurrence of each predicted bleed event under the selected treatment option by attributing weighted values to two or more bleed risk factors from said patient's medical history. In addition, the simulation assigns at least one subsequent health state for each predicted stroke event and each predicted bleed event based on the event condition of the patient and the course of treatment in the existing health state. The simulation may repeat the assigning steps for a subsequent period of life extension in the subsequent health state until the patient is predicted to die, or at least 98% of the cohort is predicted to die. The method further comprises administering to the patient the treatment option that provides the largest cumulative net benefit. Preferably, the patient suffers from atrial fibrillation.

[0008] In addition, the treatment options may comprise administration of a drug or biologic product having anticoagulant activities, such as, for example, vitamin K antagonists, antithrombin activators, factor Xa inhibitors, direct thrombin inhibitors, and glycoprotein IIb/IIIa inhibitors. The drugs may be warfarin, aspirin, or edoxaban. The treatment options may further comprise administration of a second drug or biologic product having anticoagulant activities.

[0009] In one embodiment, the Markov chain simulation comprises Monte Carlo methods. In another embodiment, the Markov chain simulation comprises expected value analysis. In another embodiment, a method of treating atrial fibrillation may be provided.

[0010] The present invention also provides a method for reducing a patient's risk of bleed under anticoagulant treatment comprising a step for determining a cumulative net benefit for each of two or more treatment options using a Markov chain simulation for predicting a cumulative period of life extension and the occurrence of stroke and bleed events during the cumulative period of life extension under a selected treatment option for a cohort of patients. The simulation comprises generating a risk profile for the patient based on the patient's medical history. The risk profile comprises a health state comprising an event condition of the patient, a course of treatment based on the event condition, a first risk score attributing weighted values to two or more stroke risk factors from said patient's medical history, and a second risk score attributing weighted values to two or more stroke bleed factors from said patient's medical history. The event condition is selected from a group consisting of lack of stroke or bleed events, recurrent and non-recurrent stroke events, recurrent and non-recurrent bleed events, and combinations of stroke events and bleed events. The course of treatment is selected from the group consisting of: (i) administration of said treatment option at one or more different dosages, (ii) temporary discontinuation of said treatment option, and (iii) permanent discontinuation of said treatment option. In addition, a numerical value of net benefit is associated with the health state. The numerical value corresponds to a period of life extension in said health state predicted by the simulation, reduced by an amount corresponding to said patient's reduction in quality of life arising from the event condition or the course of treatment for the selected treatment option. The simulation further comprises assigning a probability for the occurrence of each predicted stroke event under each treatment option corresponding to the first risk score and a probability for the occurrence of each predicted bleed event corresponding to the second risk score. In addition, the simulation assigns at least one subsequent health state for each predicted stroke event and each predicted bleed event based on the condition of said patient and the course of treatment in the existing health state. The simulation may repeat the assigning steps for a subsequent period of life extension in the subsequent health state until the patient is predicted to die, or at least 98% of said cohort is predicted to die. The method further comprises administering to the patient the treatment option that provides the largest cumulative net benefit.

[0011] In certain preferred embodiments, the first risk score attributes a weighted value of 2 to a prior stroke or prior transient ischemic attack (TIA), and a weighted value of 1 to at least one other stroke risk factor. Additionally, the second risk score attributes a

weighted value of 3 to anemia and a weighted value of either 1 or 2 to at least one other bleed risk factor. Preferably, the second risk score also attributes a weighted value of 2 to a second bleed risk factor selected from the group consisting of age, history of bleeding, and reduced level of estimated glomerular filtration rate (eGFR).

[0012] These and other aspects of the present invention will become apparent to those skilled in the art after a reading of the following detailed description of the invention, including the appended claims.

BRIEF DESCRIPTION OF THE FIGURES

[0013] Figure 1 shows an exemplary system according to the present invention.

[0014] Figure 2 shows an exemplary method for choosing one of two different treatment options for a patient.

[0015] Figure 3 shows a generalized decision flow chart for a Markov simulation for quantifying a net benefit of a particular anticoagulant treatment option.

[0016] Figure 4 shows an exemplary Markov chain for quantifying a net benefit of a particular anticoagulant treatment option, the Markov chain having a plurality of different health states.

[0017] Figure 5 shows a branch of the exemplary Markov chain of Figure 4 corresponding to Health State 1.

[0018] Figure 6 shows a branch of the exemplary Markov chain of Figure 4 corresponding to Health State 2.

[0019] Figure 7 shows a branch of the exemplary Markov chain of Figure 4 corresponding to Health State 3.

[0020] Figure 8 shows a branch of the exemplary Markov chain of Figure 4 corresponding to Health State 4.

[0021] Figure 9 shows a branch of the exemplary Markov chain of Figure 4 corresponding to Health State 5.

[0022] Figure 10 shows a branch of the exemplary Markov chain of Figure 4 corresponding to Health State 6.

[0023] Figure 11 shows a branch of the exemplary Markov chain of Figure 4 corresponding to Health State 7.

[0024] Figure 12 shows a branch of the exemplary Markov chain of Figure 4 corresponding to Health State 8.

[0025] Figure 13 shows a branch of the exemplary Markov chain of Figure 4 corresponding to Health State 9.

[0026] Figure 14 shows a branch of the exemplary Markov chain of Figure 4 corresponding to Health State 10.

[0027] Figure 15 shows a branch of the exemplary Markov chain of Figure 4 corresponding to Health State 11.

[0028] Figure 16 shows a branch of the exemplary Markov chain of Figure 4 corresponding to Health State 12.

[0029] Figure 17 shows a branch of the exemplary Markov chain of Figure 4 corresponding to Health State 13.

[0030] Figure 18 shows a branch of the exemplary Markov chain of Figure 4 corresponding to Health State 14.

[0031] Figure 19 shows a branch of the exemplary Markov chain of Figure 4 corresponding to Health State 15.

[0032] Figure 20 shows a branch of the exemplary Markov chain of Figure 4 corresponding to Health State 16.

[0033] Figure 21 shows a branch of the exemplary Markov chain of Figure 4 corresponding to Health State 17.

[0034] Figure 22 shows a branch of the exemplary Markov chain of Figure 4 corresponding to Health State 18.

[0035] Figure 23 shows a branch of the exemplary Markov chain of Figure 4 corresponding to Health State 19.

[0036] Figure 24 shows a branch of the exemplary Markov chain of Figure 4 corresponding to Health State 20.

[0037] Figure 25 shows a branch of the exemplary Markov chain of Figure 4 corresponding to Health State 21.

[0038] Figure 26 shows a branch of the exemplary Markov chain of Figure 4 corresponding to Health State 22.

[0039] Figure 27 shows a branch of the exemplary Markov chain of Figure 4 corresponding to Health State 23.

[0040] Figure 28 shows a branch of the exemplary Markov chain of Figure 4 corresponding to Health State 24.

[0041] Figure 29 shows a branch of the exemplary Markov chain of Figure 4 corresponding to Health State 25.

[0042] Figure 30 shows a branch of the exemplary Markov chain of Figure 4 corresponding to Health State 26.

[0043] Figure 31 shows a branch of the exemplary Markov chain of Figure 4 corresponding to Health State 27.

[0044] Figure 32 shows a branch of the exemplary Markov chain of Figure 4 corresponding to Health State 28.

[0045] Figure 33 shows a branch of the exemplary Markov chain of Figure 4 corresponding to Health State 29.

[0046] Figure 34 shows a branch of the exemplary Markov chain of Figure 4 corresponding to Health State 30.

[0047] Figure 35 shows a proportion of optimal treatment for base case cohort ages 74-75.

DETAILED DESCRIPTION

[0048] Patients suffering from atrial fibrillation may have an increased risk of suffering from a stroke or embolic event. Anticoagulants may be administered to patients suffering from atrial fibrillation to reduce the patient's risk for a stroke or an embolic event. Therefore, the benefits of anticoagulant treatment may be observed in the reduction of thromboembolic or ischemic events, such as, but not limited to stroke. However, anticoagulants prevent a patient's blood from coagulating, or clotting, thereby increasing the patient's risk for an adverse bleed event and/or bleeding complication, such as, for example, hemorrhage. Accordingly, the risks for anticoagulant treatment of a patient suffering from atrial fibrillation may include an increased risk, rate and/or probability of an adverse bleed event and/or bleeding complication. The present invention provides methods for choosing among two or more treatment options for a patient by weighing various risks and benefits for each potential treatment option before making a treatment determination. Preferably, the treatment options comprise administration of an anticoagulant, and more preferably, an oral anticoagulant to the patient. In other embodiments, the invention provides methods for reducing a patient's risk of stroke, methods for preventing stroke, methods for treating a patient with atrial fibrillation or methods for preventing stroke in patients with atrial fibrillation by weighing various risks and benefits for each potential treatment option before making a treatment determination.

[0049] Generally, the methods of the present invention comprises identifying an optimal treatment option from a plurality of treatment options, wherein said optimal treatment option provides the largest net benefit (i.e., differential between benefits and risks) to the patient. Preferably, the methods of the present invention would recommend or select a potential treatment option for a patient, when the benefits of the selected treatment out-weight the risks. More preferably, the methods of the present invention weights and compares the benefit of reduced thromboembolic, ischemic or stroke events to the bleeding risks associated with anticoagulant treatment before recommending and/or selecting a treatment option that provides the largest net benefit for administration to the patient. In one embodiment, the methods may evaluate treatment options, particularly anticoagulant treatment options, for a patient based on the variable stroke and bleed risks. In certain embodiments, the present invention may be used in evaluating and determining whether a patient should be treated with an anticoagulant or if the patient was more suitable for alternative treatments. Moreover, the

invention may evaluate the impact of a particular treatment recommendation by weighing the benefit of an anticoagulant treatment with bleed risks. In other embodiments, the methods of the present invention may be used as an analysis tool for medical personnel (e.g., doctors, nurses, nurse practitioners, etc.) to evaluate and quantitatively estimate the impact of an anticoagulant treatment on a patient by simulating different scenarios and comparing those scenarios to the predicted life of the patient without any treatment.

[0050] Suitable treatment options may include administration of a drug or biologic product having anticoagulant activities to a patient. More particularly, drugs or biologics products having anticoagulant activities include, for example, vitamin K antagonists (including but not limited to coumarines and indandione derivatives), antithrombin activators, factor Xa inhibitors (e.g., edoxaban, rivaroxaban, apixaban, betrixaban, darexaban, etc.), direct thrombin inhibitors (e.g., dabigatran, argatroban, hirudins, etc.), glycoprotein IIb/IIIa inhibitor, amongst others. Non-limiting examples of suitable drugs or biologic products having anticoagulant activities include: warfarin, coumatetralyl, phenprocoumon, acenocoumarol, coumetarol, cyclocoumarol, dicoumarol, ethylidene dicoumarol, tiocloamarol, ethyl biscoumacetate, anisindione, bromindione, clorindione, phenindione, clorindione, diphenadione, fluindione, heparin, low molecular weight heparin, fondaparinux, idraparinux, edoxaban, rivaroxaban, apixaban, betrixaban, darexaban, hirudin, bivalirudin, lepirudin, desirudin, argatroban, melagatran, ximelagatran, dabigatran, abciximab, eptifibatide, tirofiban, aspirin, aniclod, batroxobin, etc. The drug or biologic product may also be administered to the patient at any non-toxic dose in any suitable manner, such as, for example, intravenous, intramuscular, subcutaneous, oral, suppository, etc. Preferably, the drug or biologic product is orally administered to the patient. More preferably, the orally administered drug or biologic product may be selected from a group consisting of warfarin, aspirin, edoxaban, and other factor Xa inhibitors.

[0051] Measuring the net benefit of a potential treatment option is, however, difficult, because the risks are not necessarily equivalent in magnitude to the benefits of a potential treatment option. Bleed risks are often complex and may be difficult to quantify outside a clinical trial setting. Furthermore, the balance between ischemic strokes and bleeding events is made more complex by the fact that intra- and extracranial bleeding events have very different impacts on health. For example, reduction of risk for an ischemic or stroke event such as an ischemic stroke may not confer the same magnitude of benefit as avoidance of a

bleed, including but not limited to gastrointestinal (GI) bleeds. To provide a common basis to compare the risks and benefits of a potential treatment option, there needs to be a uniform metric for quantifying, evaluating and/or comparing risks and benefits. In some embodiments, the risks and benefits are quantified using a shared and/or uniform metric. The net benefit may also be quantified as units of benefit minus units of risk. Preferably, where a quantitative measurement of the net benefit is positive, a potential treatment option would be recommended and/or selected; and where the quantitative measurement of the net benefit is negative, a potential treatment would not be recommended and/or selected. Without being bound by any theory, it is believed that the use of an objective bleeding risk score that provides a systematic quantification of bleeding risk as compared to stroke risks may minimize overestimation of bleed risk when treating atrial fibrillation patients with anticoagulants.

[0052] The shared and/or uniform metric may comprise any quantified units suitable for quantifying health risks and benefits. Any type of metric for measuring disease burden may be used to quantify and evaluate the net benefit of any potential treatment option. Suitable metrics may include, for example, total number of stroke and/or bleed events, total number of hemorrhagic and/or embolic events, total number of hemorrhagic and/or embolic strokes, total number of major adverse events that required hospitalization, number of hospital days required, overall cost, number need to treat (NNT), quality adjusted life years (QALYs) and combinations thereof. As used herein, NNT refers to the number of patient-years of therapy that would be required to prevent a single thromboembolism.

[0053] Preferably, the risks and benefits are quantified in QALYs, which is based on the number of years of life that could be added by a potential treatment option, reduced by any deviations from perfect health or reductions in the patient's quality of life including, for example, short term morbidity and/or disability, long term morbidity and/or disability, or other limitations to the patient's quality of life, such as, for example, need for a wheelchair, cane, crutches or other mobility assistance devices, pain, restrictions on diet, strict treatment regimens, etc. QALYs provide a uniform unit for measuring disease burden based on both the quality and the quantity of life that could be added by a potential treatment option. In particular, QALYs provide a mechanism to assign less weight to minor events and more weight to severe events, thereby providing a composite utility value that can act as a score card to tally the total impact of potential risks and benefits (e.g., potential increase of

hemorrhagic risks and potential decrease of ischemic risk) on mortality and quality of life.

[0054] While any metric may be used to quantify the health risks and benefits for a particular treatment option, particularly an anticoagulant treatment option, QALYs are particularly preferred because they allow for a uniform quantitative unit for assessing varying degrees of risks and benefits for any particular treatment option and for quantifying the severity of any potential adverse events, including, for example, stroke events, bleed events, and death of patient. QALYs do not treat all adverse events with equal weights, for example, QALYs for hemorrhagic strokes may be different for QALYs for ischemic strokes, because these two different types of adverse events carry different mortality rates and present different mortality risks to the patient. In particular, QALYs can assess the risks and benefits of both major and minor events. For example, the QALY for a major adverse event, such as a severe stroke or intracranial hemorrhage, is significantly reduced, whereas the QALY for a minor adverse event, such as a minor bleed, would be greater than that for a major adverse event. The ability to assign different weights to adverse events of differing severity avoids the potential for under-treatment of a patient that could have otherwise occurred had the risk for a minor bleed been treated as equivalent to the risk for ischemic strokes. Moreover, QALYs allow for the comparison of different adverse events, which may provide a better assessment of the overall adverse risks and/or benefits for any particular treatment option. For example, QALYs provide for a uniform basis for comparison for ischemic stroke, hemorrhagic strokes, and gastrointestinal related bleeding events, which is particularly important for assessing the risks of administering warfarin to a patient, because a majority of bleeding events caused by warfarin occurs in the gastrointestinal regions.

[0055] In a preferred embodiment, the methods of the present invention provide individualized recommendations and/or selections of a potential treatment option based on a patient's individual risk factors for the occurrence of an adverse health event, such as a stroke event or a bleed event. For example, the methods may determine whether an anticoagulant treatment option, particularly administration of an oral anticoagulant, will be suitable for a particular patient based on the variable stroke and bleed risks specific for that patient. In addition, the methods may also determine a suitable course of treatment and/or dosing regimen based on the specific risk factors personal to said patient.

[0056] The risk factors for a particular patient may be part of a patient's medical history. Any factors that relate to the health of the patient, including but not limited to stroke

and bleed risk factors maybe used to assess the specific risks and/or benefits of an anticoagulant treatment option for a particular patient. In some embodiments, the risk factors may be based on the health of the patient at any time. In other embodiments, the risk factors may be based on the patient's health with a limited time period, such as, 6, 12, 18 or 24 months prior to initiating treatment or index atrial fibrillation diagnosis.

[0057] Examples of stroke risk factors include, but not limited to, prior stroke (e.g., ICD-9-CM code 433.**-434.**), transient cerebral ischemia (e.g., CCS category 112, ICD-9-CM code 435.0, 435.1, 435.2, 435.3, 435.8 and 435.9), hypertension (e.g., ICD-9-CM code 401.**-405.**), diabetes (e.g., ICD-9-CM code 250.0*-250.8*), expanded diabetes (e.g., ICD-9-CM code 249.**, 250.9*, 790.2, 790.21, 790.22, 790.29, 791.5, 791.6), heart failure (e.g., ICD-9-CM code 398.91, 402.01, 402.11, 425.1, 425.4, 425.7, 428.0*-428.9*), coronary heart disease (e.g., ICD-9-CM code 410.**-414.**), age (e.g., ≥ 75 years), etc. as shown below in Table 1. In some embodiments, the patient's medical history may include two, three, four, five or more stroke risk factors.

Table 1.

CCS Categories	ICD-9-CM Codes
Prior stroke	433.** - 434.**
Transient cerebral ischemia [112.]	435.0, 435.1, 435.2, 435.3, 435.8, 435.9
Hypertension	401.** - 405.**
Diabetes	250.0* - 250.8*
Expanded diabetes	249.**, 250.9*, 790.2, 790.21, 790.22, 790.29, 791.5, 791.6
Heart failure	398.91, 402.01, 402.11, 425.1, 425.4, 425.7, 428.0* - 428.9*
Coronary heart disease	410.** - 414.**

[0058] Additionally, bleed risk factors may include, for example, prior stroke, anemia, renal failure wherein creatinine ≥ 1.5 , history of cancer, history of any bleeding, prior gastrointestinal hemorrhage, age (e.g., ≥ 75 years), etc. Other exemplary bleed risk factors are provide in Table 2 with the corresponding CCS Categories and/or ICD-9-CM codes. In some embodiments, the patient's medial history may include two, three, four, five or more, stroke risk factors.

Table 2.

Exemplary Bleed Risk Factors	
PRIOR STROKE	
433.** - 434.**	
Anemia	59, 60, 61
4.1.1 Acute posthemorrhagic anemia [60.]	
	285.1
4.1.2 Sickle cell anemia [61.]	
	282.41, 282.42, 282.5, 282.60, 282.61, 282.62, 282.63, 282.64, 282.68, 282.69
4.1.3 Deficiency and other anemia [59.]	
4.1.3.1 Iron deficiency anemia	
	280.1, 280.8, 280.9
4.1.3.2 Other deficiency anemia	
	281.0, 281.1, 281.2, 281.3, 281.4, 281.8, 281.9
4.1.3.3 Aplastic anemia	
	284.0, 284.01, 284.09, 284.1, 284.8, 284.81, 284.89, 284.9
4.1.3.4 Chronic blood loss anemia	
	280.0
4.1.3.5 Acquired hemolytic anemia	
	283.0, 283.1, 283.10, 283.11, 283.19, 283.2, 283.9
4.1.3.6 Other specified anemia	
	282.0, 282.1, 282.2, 282.3, 282.4, 282.49, 282.7, 282.8, 282.9, 284.2, 285.0, 285.21, 285.22, 285.29, 285.8
4.1.3.7 Anemia; unspecified	
	285.9
“RENAL FAILURE” Creatinine $\geq$ 1.5	
10.1.2 Acute and unspecified renal failure [157.]	157
10.1.2.1 Acute renal failure	
	5845, 5846, 5847, 5848, 5849
10.1.2.2 Unspecified renal failure	
	586
10.1.3 Chronic renal failure [158.]	
	585, 585.3, 585.4, 585.5, 585.6, 585.9, 792.5, V42.0, V45.1, V45.11, V45.12, V56.0, V56.1, V56.2, V56.31, V56.32, V56.8
HISTORY OF CANCER	
2. Neoplasms (excluding non-melanoma skin cancers) 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47	
ICD9-CM: 141-172.** and 174-208.**	
HISTORY OF ANY BLEEDING	
Prior Intracranial Hemorrhage	
430.**, 431.**, 432.**, 852.0*, 852.2*, 852.4*, 853.0*	
Prior gastrointestinal hemorrhage	
455.2 Internal hemorrhoids with other complication	
455.5 External hemorrhoids with other complication	
455.8 Unspecified hemorrhoids with other complication	
456.0 Esophageal varicies with bleeding	
456.20 Esophageal varicies in diseases classified elsewhere with bleeding	
459.0 Hemorrhage, unspecified	

530.7 Gastroesophageal laceration-hemorrhage syndrome
530.82 Esophageal hemorrhage
531.00 Acute gastric ulcer with hemorrhage without mention of obstruction
531.01 Acute gastric ulcer with hemorrhage with obstruction
531.20 Acute gastric ulcer with hemorrhage and perforation without mention of obstruction
531.21 Acute gastric ulcer with hemorrhage and perforation with obstruction
531.40 Chronic or unspecified gastric ulcer with hemorrhage without mention of obstruction
531.41 Chronic or unspecified gastric ulcer with hemorrhage with obstruction
531.60 Chronic or unspecified gastric ulcer with hemorrhage and perforation without mention of Obstruction
531.61 Chronic or unspecified duodenal ulcer with hemorrhage and perforation with obstruction
533.00 Acute peptic ulcer, site unspecified, with hemorrhage without mention of obstruction
533.01 Acute peptic ulcer, site unspecified, with hemorrhage with obstruction
533.20 Acute peptic ulcer, site unspecified, with hemorrhage and perforation without mention of obstruction
533.21 Acute peptic ulcer, site unspecified, with hemorrhage and perforation with obstruction
533.40 Chronic or unspecified peptic ulcer, site unspecified, with hemorrhage without mention of obstruction
533.41 Chronic or unspecified peptic ulcer, site unspecified, with hemorrhage with obstruction
533.60 Chronic or unspecified peptic ulcer, site unspecified, with hemorrhage and perforation without mention of obstruction
533.61 Chronic or unspecified peptic ulcer, site unspecified, with hemorrhage and perforation
534.00 Acute gastrojejunal ulcer with hemorrhage without mention of obstruction
534.01 Acute gastrojejunal ulcer with hemorrhage with obstruction
534.20 Acute gastrojejunal ulcer with hemorrhage and perforation without mention of obstruction
534.21 Acute gastrojejunal ulcer with hemorrhage and perforation with obstruction
534.40 Chronic or unspecified gastrojejunal ulcer with hemorrhage without mention of obstruction.
534.41 Chronic or unspecified gastrojejunal ulcer with hemorrhage with obstruction
534.60 Chronic or unspecified gastrojejunal ulcer with hemorrhage and perforation without mention of obstruction
534.61 Chronic or unspecified gastrojejunal ulcer with hemorrhage and perforation with obstruction
535.01 Acute gastritis with hemorrhage
535.11 Atrophic gastritis with hemorrhage
535.21 Gastric mucosal hypertrophy with hemorrhage
535.31 Alcoholic gastritis with hemorrhage
535.41 Other specified gastritis with hemorrhage
535.51 Unspecified gastritis and gastroduodenitis with hemorrhage
535.61 Duodenitis with hemorrhage
537.83 Angiodysplasia of stomach and duodenum with hemorrhage (added 12/4/00)

562.02 Diverticulosis of small intestine with hemorrhage
562.03 Diverticulitis of small intestine with hemorrhage
562.12 Diverticulosis of colon with hemorrhage
562.13 Diverticulitis of colon with hemorrhage
568.81 Hemoperitoneum (nontraumatic)
569.3 Hemorrhage of rectum and anus
569.85 Angiodysplasia of intestine with hemorrhage
578 Gastrointestinal hemorrhage
578.0 Hematemesis
578.1 Blood in stool
578.9 Hemorrhage of gastrointestinal tract, unspecified
Other Prior Hemorrhage
Prior other hemorrhage may be defined as a primary discharge diagnosis of hemopericardium, vascular disorders of kidney, hematuria, hemarthrosis, epistaxis, or hemoptysis based on the following ICD-9 codes:
423.0 Hemopericardium
459.0 Hemorrhage, unspecified
593.81 Vascular disorders of the kidney
719.1 Hemarthrosis
719.10 Hemarthrosis: site unspecified
719.11 Hemarthrosis: shoulder region
719.12 Hemarthrosis: upper arm
719.13 Hemarthrosis: forearm
719.14 Hemarthrosis: hand
719.15 Hemarthrosis: pelvic region and thigh
719.16 Hemarthrosis: lower leg
719.17 Hemarthrosis: ankle and foot
719.18 Hemarthrosis: other specified sites
719.19 Hemarthrosis: multiple sites
784.7 Epistaxis
784.8 Hemorrhage from throat (added 12/4/00)
786.3 Hemoptysis
599.7 Hematuria

[0059] These risk factors may relate to a probability of an adverse event, which may include without limitation a stroke event, a bleed event (e.g., intracranial or gastrointestinal bleed event), a thromboembolic event, a fatal event, among others. Preferably, the risk factors relate to stroke events and/or bleed events. Because each risk factor may contribute a different degree of risk to a patient, it is more preferred that the risk factors are assigned weighted values to reflect their relative contributions to a patient's risk for an adverse event, such as, for example, a stroke or bleed event. For example, a first stroke risk factor (e.g., a prior stroke or transient ischemic attack) may be assigned a higher weighted value than a second stroke risk factor (e.g., greater than 75 years old, hypertension, diabetes mellitus, or

heart failure) representing an increased probability that a patient having the first stroke risk factor would experience a stroke event as compared to a patient having the second stroke risk factor, but not the first stroke risk factor. In a similar example, a first bleed risk factor (e.g., anemia) may be assigned a higher weighted value than a second bleed risk factor (e.g., greater than 75 years old, having a history of bleeding, or eGFR < 30) representing an increased probability that a patient having the first bleed risk factor would experience a bleed event as compared to a patient having the second bleed risk factor, but not the first bleed risk factor.

[0060] Stroke events may include, for example, various degrees of ischemic stroke (e.g., ICD-9-CM code 43.00-.01, 433.10-.11, 433.20-.21, 433.30-.31, 434.00-.01, 434.10-11, 434.90-.91), acute, ill-defined cerebrovascular disease (e.g., ICD-9-CM code 436), other thromboembolic event (e.g., ICD-9-CM code 444.0, 444.1, 444.21-22, 444.81, 444.89, 557.0, 557.1, 557.9), transient cerebral ischemia (e.g., CCS Category 112., ICD-9-CM code 435.0, 435.1, 435.2, 435.2, 435.3, 435.8, 435.9), etc. Preferably, the stroke events comprise fatal ischemic stroke, severe ischemic stroke, mild ischemic stroke, and/or reversible ischemic stroke.

[0061] Bleed events may include, for example, various degrees of intracranial hemorrhage (e.g., ICD-9-CM code 430, 431, 432.0, 432.1, 432.9, 852.0, 852.2, 852.4, 853.0), GI hemorrhage (e.g., ICD-9-CM code 455.2, 455.5, 455.8, 456.0, 456.20, 459.0, 530.7, 530.82, 531.00-01, 531.20-21, 531.40-41, 531.60-61, 532.00-01, 532.20-21, 532.40-41, 532.60-51, 533.00-01, 533.20-21, 533.40-41, 533.60-61, 534.00-01, 534.20-.21, 534.40-41, 534.60-61, 535.01, 535.11, 535.21, 535.31, 535.41, 535.51, 535.61, 537.83, 562.02, 562.03, 562.12, 562.13, 568.81, 569.3, 569.85, 578.0, 578.1, 578.9), hemopericardium (e.g., ICD-9-CM code 423.0), vascular disorders of kidney (e.g., ICD-9-CDM code 593.81), hematuria (e.g., ICD-9-CM code 599.7), hemarthrosis (e.g., ICD-9-CM code 719.11, including fifth digits 0-9), epistaxis (e.g., ICD-9-CM code 784.7), hemorrhage from throat (e.g., ICD-9-CM code 784.8), hemoptysis (e.g., ICD-9-CM code 786.3), etc. In a preferred embodiment, bleed events comprise fatal hemorrhage, intra-cranial hemorrhage, major non-cranial hemorrhage (i.e., non-cranial hemorrhage requiring hospital stay), particularly gastrointestinal hemorrhage, and/or minor hemorrhage, such as bleed events that may cause pain or discomfort, but does not require hospital stay for the treatment or management of the minor hemorrhage.

[0062] In one embodiment, the patient's risk factors may be used to establish a baseline risk profile. The baseline risk profile provides a patient's general level of risk for a stroke or bleed event under a particular treatment option. The baseline risk profile may be adjusted based on the selected treatment option or specific triggering events, such as the predicted occurrence of an adverse event, including but not limited to stroke events, bleed events, and/or other illnesses. In some embodiments, the baseline risk profile may be adjusted by a numerical factor representing a relative risk of a particular treatment option as compared to the baseline risk profile (e.g., relative risk of stroke and/or bleed events of no treatment vs. aspirin, relative risk of stroke and/or bleed events of warfarin vs. aspirin, relative risk of recurrent stroke vs. baseline stroke risk, etc.).

[0063] For example, stroke risk factors may be used to determine a baseline stroke risk for a particular patient. In some embodiments, each of two or more stroke risk factors may be assigned a weighted score reflecting the relative risk of stroke events predicted to be contributed by each stroke risk factor. The weighted score may correspond to different levels of risk for stroke events. The correlation between the weighted scores and the different levels of risk for stroke events may be established by any suitable means. The weighted scores may be assigned probabilities for stroke events based on information published in the literature or prophetically assigned by one skilled in the art. For example, a low weighted score may correspond to a low risk for stroke events, whereas a high weighted score may correspond to a high risk for stroke events. In some embodiments, the weighted score may correspond linearly or non-linearly (e.g., logarithmically or exponentially) to a probability or rate for stroke events. Preferably, the correlation between the weighted scores and the probabilities for stroke events may be established from historical medical data, published data, or combinations thereof. Specifically, statistical analysis may be performed on historical medical data, published data, or combinations thereof to assigned empirical probabilities to the weighted scores. One example of a scheme for assigning probabilities for stroke events to the weighted scores is the CHAD₂ stroke-risk index described by O'Brien, et al., "Cost and Effectiveness of Ximelagatran for Stroke Prophylaxis in Chronic Atrial Fibrillation," JAMA, Vol. 293, No. 6, 699-706 (2005) and Gage, et al., "Validation of Clinical Classification Schemes for Predicting Stroke: Results From the National Registry of Atrial Fibrillation," JAMA, Vol. 285, No. 22, 2864-2870 (2001), which is also further described in Example 1.

[0064] In some embodiments, the baseline risk profile, established based on the patient's risk factors, may also include bleed risk factors. For example, each of two or more bleed risk factors may be assigned a weighted score reflecting the relative risk of bleed events predicted to be contributed by each bleed risk factor. The weighted score may correspond to different levels of risk for bleed events. The correlation between the weighted scores and the different levels of risk for bleed events may be established by any suitable means. The weighted scores may be assigned probabilities for bleed events based on information published in the literature or prophetically assigned by one skilled in the art. For example, a low weighted score may correspond to a low risk for bleed events, whereas a high weighted score may correspond to a high risk for bleed events. In some embodiments, the weighted score may correspond linearly or non-linearly (e.g., logarithmically or exponentially) to a probability or rate for bleed events. Preferably, the correlation between the weighted scores and the probabilities for bleed events may be established from historical medical data, published data, or combinations thereof. Specifically, statistical analysis may be performed on historical medical data, published data, or combinations thereof to assign empirical probabilities to the weighted scores. One example of a scheme for assigning probabilities for bleed events to the weighted scores of the bleed risk factors is the ATRIA bleed-risk indices further described below in Example 2 and Example 3. While bleeding risk provides an important dimension to medical decision making in anticoagulation, the ultimate decision to treat must consider the ischemic event risk since this is the very reason for anticoagulant treatment.

[0065] In some embodiments, the methods comprise quantifying a net benefit of a treatment option by modeling the probabilities for stroke and bleed events. Incorporating risk and benefit evaluations of both stroke and bleed risk and prevention allows for a more accurate assessment of the risks and/or benefits of anticoagulant treatment and improves treatment decisions between promising new agents that may have different bleed risks as compared to warfarin. The model may be used to provide an analysis of the risks and benefits for a particular treatment option. Preferably, said stroke and bleed events include recurring and non-recurring embolic and/or hemorrhagic events. In another embodiment, the net benefit of a treatment option may be quantified by an iterative simulation. In other embodiments, the simulation is recursive. Preferably, the simulation comprises a stochastic process. More preferably, the simulation comprises a discrete random process over time, by which is meant that the process is at a certain state at each specific time, with the state of the

process changing randomly between iterations along a discrete time line. In some embodiments, a subsequent state in a discrete random process over time depends on the existing state. For example, the simulation may comprise a Markov chain, which is a discrete random process with the property that the next state depends on the current state, and particularly useful for simulating natural development of chronic diseases.

[0066] A Markov model assumes that a patient is in one of a finite number of discrete health states at a given point in time. Probabilistic transitions from one health state to another can happen over time and may be based on patient demographics, stroke and bleeding risk profiles at the time of atrial fibrillation diagnosis, and stroke prevention treatment as available from published sources. In certain embodiments, for each patient in the simulated cohort, the simulations provides a treatment recommendation if the estimated quality-adjusted life years (QALY) was higher for the selected treatment than other options over the course of lifetime treatment.

[0067] In one particular embodiment, the simulation may comprise a Markov chain simulation of various different health states of a patient iterated over a discrete time line. For each period of life extension predicted by said simulation, the patient would gain a numerical value, representing a metric of benefit, reflecting the patient's quality of life for the health state of the patient during each fixed period of life extension. For example, if a patient is predicted to be well and would not need to continue treatment, the patient may accrue the full benefit, i.e., the full numerical value, for the period of life extension predicted by the simulation. Alternatively, if a patient is predicted to suffer from an adverse event that may result in long term morbidity, e.g., moderate or severe stroke, intra-cranial hemorrhage, mild stroke, recurrent stroke or bleed, etc., the numerical value for the period of life extension and all predicted periods of life thereafter would be significantly reduced to reflect the predicted long-term reduction in quality of life for the patient. If a patient is predicted to suffer from an adverse event that may result in short term morbidity, e.g., major non-cranial bleed, reversible stroke, minor bleed, etc., the numerical value for the period of life extension predicted, but not necessarily predicted periods of life thereafter, would be reduced by a lesser amount, reflecting a reduced level of morbidity and the predicted short-term reduction in quality of life for the patient. In some embodiments, the simulation may iterate every fixed period, corresponding to a fixed period of life extension predicted by said simulation, unless

the patient is predicted to die. For example, the simulation may iterate every month, every 2 months, every 3 months, every 6 month or every year.

[0068] Each health state may comprise a condition of the patient, which may include the stroke and/or bleed state of a patient, the patient being in a well state, or the patient having suffered a fatal event, and course of treatment for the patient, including whether the patient continues or discontinues (permanently or temporarily) a particular treatment option. Exemplary stroke states include, but are not limited to severe ischemic stroke, moderate ischemic stroke, mild ischemic stroke, reversible ischemic stroke, and having had a prior reversible stroke. Exemplary bleed states include, but are not limited to intra-cranial hemorrhage, major non-cranial hemorrhage, minor hemorrhage and having had a prior major non-cranial hemorrhage. The probabilities for stroke and bleed events as a function of the stroke and bleed risk factors, respectively, may be established from historical medical data, published data, or combinations thereof. In one particular embodiment, the probabilities for stroke and bleed events are established by statistical analysis of a pool of data stored within a computing device or from a database remotely accessible via a communications network. Based on the risk factors obtained from the patient medical history and the current health state of the patient, the probability of each possible subsequent health state may be predicted.

[0069] Preferably, the simulation is conducted using Monte Carlo methods, which are a class of computations algorithms that utilize repeated random sampling to predict possible results. In some embodiments, simulation is conducted using Monte Carlo methods for a cohort of patients (each member of the cohort may be computer simulated and may be identical), for example, the size of the cohort may be at least 100, at least 500, at least 1,000, at least 2,500, at least 5,000, or at least 10,000. The simulation may be terminated when substantially all of the cohort reach a predicted fatal event, such that further predictions for the remainder of the cohort do not significantly change the cumulative net benefit predicted by the simulation. For example, the simulation may terminate when at least 90%, at least 95%, at least 97%, at least 98%, at least 99% or at least 99.9% of said cohort reaches a predicted fatal event.

[0070] In certain embodiments, the methods of the present invention may be executed by a processor, typically on a general or specific purpose computing device or network of computing devices. Suitable computing devices include, for example, single-processor or multiprocessor computer systems, minicomputers, mainframe computers, as well as personal

computers, hand-held computing devices, microprocessor-based or programmable consumer electronics, and the like. In some embodiments, the computing device may be portable, by which it meant that the device can be readily moved from one location to another by a single user, such as, for example, laptop computers, tablet computers, netbooks, personal digital assistants (PDA), cellular phones, smart phones, etc.

[0071] In particular, the methods may be presented in terms of computer-executable instructions stored on any suitable computer readable medium. Moreover, the methods may be a computer program module and may optionally be capable of being implemented in combination with other program modules. Computer program modules may include, for example, routines, programs, components, data structures, etc. that perform particular tasks and/or implement particular abstract data types. In addition, the computer program modules may include any computer software packages for performing decision analysis and/or simulating a Markov chain, using any algorithm, including Monte Carlos analysis and expected value analysis. One particularly suitable computer package is the TreeAge Pro decision analysis software by TreeAge Software, Inc. However, any suitable decision analysis software may be used.

[0072] Suitable computer-readable media may include, for example, computer storage media and communication media. Computer storage media may include volatile and non-volatile, removable and non-removable media implemented in any method or technology for storage of information such as computer-readable instructions, data structures, program modules or other data, which includes, for example, RAM, ROM, EPROM, EEPROM, flash memory or other solid state memory technology, CD-ROM, DVD, or other optical storage, magnetic cassettes, magnetic tape, magnetic disk storage or other magnetic storage devices, or any other medium which can be used to store the desired information and which can be accessed by the computing device or network of computing devices.

[0073] Figure 1 shows an exemplary system **10** according to the present invention. The system **10** may include a communications network **2** (e.g., Internet). The communications network **2** may be in communication with a database **4** and at least one computing device with an interface with a user **6**, such as, for example, a computer, including a desktop computer (not shown), a laptop computer **8**, a tablet computer **9**, or any portable computing devices (not shown). The database **4** and the at least one computing device may be connected to the communications network **2** via any suitable communications link **8**, such

as a wireless network **10** or a cellular network (not shown). The database **4** may be located on a computer, a server, or any other computer-readable or computer-accessible medium for electronically storing and electronically accessing a database of information. The database may include electronic medical records (EMRs) of patients, which may include risk factors for stroke or bleed events. The EMRs may be stored in the database **4** in any computer-readable form and may be remotely accessible by a user **6**, such as, for example, a physician, a nurse, or other medical personnel, via the communications network **2** from any computing device, such as a computer, particularly a desktop computer (not shown), a laptop computer **4**, a tablet computer **6** or any portable computing devices (not shown). The computing device may comprise a user interface, such as a graphical user interface (GUI) for receiving an input from the user **6** and for displaying an output to the user **6**. The user interface may be particularly suitable for providing a listing of risk factors, particularly stroke and/or bleed risk factors and receiving a boolean input from the user **6** associated with each risk factor being associated to a boolean data type. The computing device may further comprise a processor and a computing module for choosing one of two different treatment options for a patient or for quantifying a net benefit of an anticoagulant treatment using a Markov chain simulation. The computing module may comprise computer-executable instructions for choosing one of two different treatment options for a patient or for quantifying a net benefit of an anticoagulant treatment using a Markov chain simulation stored on any suitable computer readable medium. The computing module may optionally be capable of being implemented in combination with other computer program modules. Moreover, the computing module may obtain a patient's stroke and/or bleed risk factor by obtaining manual input from a user **6** through the user interface, electronically (automatically or following an input prompt by the user **6**) retrieve a patient's stroke and/or bleed risk factors from the patient's EMR stored in the database **4**, or a combination thereof. The patient's stroke and/or bleed risk factors may be processed by the processor according to the computing module to provide an output of a recommended treatment option or an output of a quantitative value corresponding to a net benefit of a treatment option, particularly an anticoagulant treatment.

[0074] Figure 2 illustrates an exemplary method for choosing one of two different treatment options for a patient. However, it is contemplated that the exemplary method of Figure 2 may be expanded to choosing from more than two different treatment options. The exemplary method of Figure 2 may be executed by any suitable processor and/or computing device. A first step **70** in the exemplary method of Figure 2 comprises obtaining a patient's

medical history data, which includes the patient's risk factors for adverse events, such as but not limited to stroke and/or bleed events. In some embodiments, the patient's medical history data may be obtained by retrieving the patient's medical records (e.g., electronic medical records (EMRs) from a computer readable medium, such a portable storage medium or a database. In certain embodiments, the computer readable medium may be remote from the computing device and connected to said computing device via a communications network, such as for example, the Internet, intranets, wireless networks, LAN, WAN, Bluetooth networks, fiber optic networks, existing telephone networks, cable networks, and other networks for communications or transfer of computer-readable and computer-accessible data. In other embodiments, the patient's medical history data may be inputted to the computing device by a user such as medical personnel (e.g., doctors, nurses, nurse practitioners, etc.) via a user interface. The user, particularly medical personnel, may provide input based on examination of the patient, interview of the patient, and/or review of the patient's medical records. Any suitable user interface, including, for example, graphical user interfaces (GUIs) for receiving data input may be used. In a particular embodiment, the user interface may comprise a listing of risk factors, particularly stroke and/or bleed risk factors; each risk factor being associated to a boolean data type (e.g., true or false, yes or no). The user may select the appropriate boolean values to input the appropriate risk factors for a particular patient.

[0075] The obtained medical history data may be used in a subsequent step **72** to generate a weighted value of net benefit for a first treatment option. Alternatively, the medical history data may be used in an alternative step **74** to generate a weighted value of net benefit for a second treatment option. Preferably, steps **72** and **74** comprise using a Markov chain Monte Carlo simulation for generating a weighted value of net benefit for each treatment option. More preferably, the weighted value of net benefit may be quantified in terms of QALYs. The first and second treatment options may include administration of a drug or biologic product having anticoagulant activities at any non-toxic dosage to a patient. For example, a first treatment option may comprise administration of warfarin and a second treatment option may comprise administration of aspirin. In step **76**, the net benefit of the first treatment option is compared to the net benefit of the second treatment option. If the weighted value for net benefit for the first treatment option is greater than the weighted value for the net benefit for the second treatment option, then the patient is administered the first treatment option (step **78**). Otherwise, the patient is administered the second treatment option (step **80**).

[0076] In certain embodiments, the methods of the present invention may be incorporated in the analysis of health insurance claims. For example, the present invention may provide a risk analysis model for insurance evaluations based on the stroke and bleed risk variables for a cohort of subjects with atrial fibrillation. Alternatively, the present invention may be utilized by a health insurance provider as an objective basis for reviewing actual practice by physicians in the treatment of atrial fibrillation in a population of patients insured by the health insurance provider. In particular, the present invention may be useful in determining the shift in proportion of patients recommended for treatment with an anticoagulant in view of a balanced consideration of ischemic and bleeding risk rates.

EXAMPLES

EXAMPLE 1: CHADS₂ STROKE-RISK INDEX

[0077] In an exemplary embodiment, the stroke risks are assessed using the CHADS₂ scores and probabilities. The specific stroke risk factors for the CHADS₂ scores are provided below in Table 3, along with the weighted score values for each of the stroke risk factors.

Table 3.

Stroke Risk Factor	CHADS ₂ Score Points
Prior stroke or TIA	2
Age $\geq$ 75 years	1
Hypertension	1
Diabetes mellitus	1
Heart Failure	1

[0078] Using the CHADS₂ scores and probabilities a patient can be assigned a risk score of 0-6 according to the presence of the stroke risk factors. In some embodiments, a patient may be assigned a CHADS₂ score based on the patient's stroke risk factors existing at any time or within a limited time period, such as, 6, 12, 18 or 24 months prior to initiating treatment or index atrial fibrillation diagnosis. Preferably, the patient is assigned a CHADS₂ score based on the patient's stroke risk factors 12 months prior to index atrial fibrillation diagnosis. Each risk score corresponds to an annual stroke rate, which are presented in Table 4. In addition, the risk scores may also be categorized into "low," "moderate," and "high" risks as shown below in Table 4.

Table 4.

CHADS ₂ Score	Stroke Rate (per 100 patient years)	Risk Category
0	1.9	Low
1	2.8	
2	4.0	Moderate
3	5.9	
4	8.5	High
5	12.5	
6	18.2	

[0079] For CHADS₂ scores based on patients receiving no anticoagulation treatment, such as those described by O'Brien, et al., "Cost and Effectiveness of Ximelagatran for Stroke Prophylaxis in Chronic Atrial Fibrillation," JAMA, Vol. 293, No. 6, 699-706 (2005) and Gage, et al., "Validation of Clinical Classification Schemes for Predicting Stroke: Results From the National Registry of Atrial Fibrillation," JAMA, Vol. 285, No. 22, 2864-2870 (2001), the stroke rates may be further adjusted by the relative risk data for each type of treatment (e.g., warfarin versus aspirin versus no treatment obtained from meta-analyses of clinical trials) to obtain treatment-specific baseline stroke rates. A listing of the relative risks for warfarin versus aspirin versus no treatment obtained from meta-analyses of clinical trials is provided below in Table 5. However, it is contemplated that the stroke rates may be adjusted by the relative risk data for any type of anticoagulant treatment (e.g., warfarin versus aspirin versus edoxaban versus no treatment) to obtain treatment-specific baseline stroke rates.

Table 5.

Relative Stroke Risks	Relative Risk Factor
Relative risk of stroke with no treatment vs. aspirin	1.3
Relative risk of stroke with warfarin vs. aspirin	0.48

[0080] Additional assumptions and adjustment may also be made based any other clinical data, whether obtained empirically or from published data. For example, a listing of additional exemplary stroke assumptions and adjustments are provided below in Table 6.

Table 6.

Stroke Assumptions	Stroke Rate Adjustments
<i>With warfarin</i>	
Reversible	9.1%
Mild	42.5%
Moderate/severe	40.2%
Fatal	8.2%
<i>With aspirin</i>	
Reversible	11%
Mild	41%
Moderate/severe	30%
Fatal	17.9%
Risk of recurrent stroke	2x baseline
Mortality rate of recurrent stroke (vs no prior stroke)	1.5x
Adjustment in risk of stroke over lifetime (by decade of life)	1.8

EXAMPLE 2: ATRIA BLEED-RISK INDEX

[0081] In an exemplary embodiment, the bleed risks are assessed using the ATRIA scores and probabilities. The specific bleed risk factors for the ATRIA scores are provided below in Table 7, along with the weighted score values for each of the five bleed risk factors: anemia (3 points), severe renal disease (e.g., estimated glomerular filtration rate < 30 ml/min or dialysis-dependent)(3 points), age ≥ 75 (2 points), prior hospitalization for bleeding (1 point), and hypertension (1 point).

Table 7.

Bleed Risk Factor	ATRIA Score Points
Anemia	3
Severe renal disease (<i>i.e.</i> , eGFR < 30)	3
Age $\geq$ 75 years	2
History of any bleeding	1
History of Hypertension	1

[0082] The ATRIA scores and probabilities are based on empirical data derived from patients on warfarin and therefore, provide a baseline for warfarin administration. Specifically, the alternative ATRIA scores and probabilities were based on data from 9,186 individuals with atrial fibrillation contributing 32,888 person-years of follow-up on warfarin. Clinical data and incident hospitalizations for major hemorrhage were obtained from clinical databases and hemorrhage events. Using variable selection through bootstrapping and split sample testing, the risk index described in this example was developed using demographic, clinical, and laboratory variables. The annualized hemorrhage rate ranged from 0.4% (0 points) to 17.3% (10 points). The c-statistic for the continuous risk score was 0.74. Collapsing points into a 3-category risk index, the major hemorrhage rate was 0.8% in the low risk group (0-3 points), 2.6% in moderate risk (4 points), and 5.8% in high risk (5-10 points); using this categorization scheme, 82.6% of the cohort person-time was considered low risk and 10.2% high risk.

[0083] Each of the bleed risk factors in the ATRIA model is assigned a score value, where a patient may be assessed a score from 0-10 points based on the bleed risk factors present in the patient's medical history. The ATRIA scores correspond to annual rates of major hemorrhage, which are provided below in Table 8. In addition, the percentage cohort in person-years is also reflected below in Table 8.

Table 8.

Alternative ATRIA Score	% Cohort Person-yrs	Major Hemorrhage Rate (% per year)
0	16.1	0.4
1	22.3	0.6
2	16.9	1.0
3	27.3	1.0
4	7.2	2.6
5	3.0	5.7
6	5.2	5.0
7	1.3	5.2
8	0.2	9.6
9	0.5	12.4
10	0.1	17.3

[0084] In addition, the bleed rates may be further adjusted to reflect the relative risk for each type of bleed or hemorrhage event. In certain exemplary embodiments, it is estimated that about 12% of major bleeding events (which includes intracranial hemorrhages (ICHs) and major extracranial hemorrhages (ECHs)) were ICHs at each level of ATRIA score. A listing of the relative risks for ICH or ECH with warfarin versus aspirin versus no treatment obtained from meta-analyses of clinical trials is provided below in Table 9. However, it is contemplated that the bleed rates may be adjusted by the relative risk data for any type of anticoagulant treatment (e.g., warfarin versus aspirin versus edoxaban versus no treatment) to obtain treatment-specific baseline stroke rates.

Table 9.

Relative Bleed Risks	Relative Risk Factor
Relative risk of ICH with aspirin vs. warfarin	0.64
Relative risk of ICH with no treatment vs. warfarin	0.44
Relative risk of major ECH with no treatment vs. warfarin	0.42
Relative risk of major ECH with aspirin vs. warfarin	0.50

[0085] In another exemplary embodiment, it may be estimated that a minor bleeding rate for patients with no bleeding risk factors is 11.8% and progressively increased to 40% for patients with the presence of all bleeding risk factors. Additional assumptions and adjustment may also be made based any other clinical data, whether obtained empirically or

from published data. For example, a listing of additional exemplary bleed assumptions and adjustments are provided below in Table 10.

Table 10.

Bleed Assumptions	Bleed Rate Adjustments
Minor bleeding without bleeding risk factor	11.8%
Minor bleeding with all bleeding risk factors	40%
<i>Fatal ICH events</i>	
With warfarin	51.6%
With ASA	25.9%
Either warfarin or ASA	1.5%
Adjustment of baseline bleeding rates (first cycle only) of patients with previous bleeding	1.5x
Risk of death from bleeding in patients with recurrent major bleeding event	1.5x
Adjustment in risk of bleeding over lifetime (per decade of life)	1.3x

EXAMPLE 3: ALTERNATIVE ATRIA BLEED-RISK INDEX

[0086] In another exemplary embodiment, the bleed risks may be assessed using an alternative risk stratification scheme similar to the ATRIA stratification discussed above in Example 2. The specific bleed risk factors for the ATRIA scores are provided below in Table 11, along with the weighted score values for each of the bleed risk factors.

Table 11.

Bleed Risk Factor	ATRIA Score Points
Anemia	3
Age $\geq$ 75 years	2
History of any bleeding	2
eGFR $<$ 30	2
History of Hypertension	1

[0087] The ATRIA scores and probabilities are based on empirical data derived from patients on warfarin and therefore, provide a baseline for warfarin administration. Each of the bleed risk factors in the ATRIA model is assigned a score value, where a patient may be assessed a score from 0-10 points based on the bleed risk factors present in the patient's

medical history. The ATRIA scores correspond to annual rates of major hemorrhage, which are provided below in Table 12. In addition, the risk scores may also be categorized into “low,” “moderate,” and “high” risks as shown in Table 12.

Table 12.

ATRIA Score	Bleed Rate (per 100 patient years)	Risk Category
0	0.340	Low
1	0.461	
2	0.775	Moderate
3	0.932	
4	3.256	High
5	3.204	
6	5.086	
7	6.231	
8	9.070	
9	9.070	
10	9.070	

EXAMPLE 4: COMBINING STROKE-RISK INDEX WITH BLEED-RISK INDEX

[0088] Combining a stroke risk index, such as the CHADS₂ index, with a bleed-risk index, such as the ATRIA index (Example 2), or the alternative index of Example 3, allows for the development of a composite risk matrix for numerous different types of patients. For example, the CHADS₂ index in combination with the ATRIA index (Example 2), or the alternative index of Example 3, may identify 64 different types of patients, shown below in Table 13. These 64 different types of patients represent combinations of different levels of risk for stroke and different levels of risk for bleed. In one particular model, there may be a hypothetical cohort comprising 64 patients, each corresponding to the available stroke and bleed risk combination shown in the matrix of Table 13.

Table 13.

CHADS ₂ Score	High	6	NA	NA	NA	60	NA	61	NA	62	63	NA	64
		5	NA	50	51	52	53	54	55	56	57	58	59
		4	39	40	41	42	43	44	45	46	47	48	49
	Mo	3	28	29	30	31	32	33	34	35	36	37	38

		2	17	18	19	20	21	22	23	24	25	26	27	
	Low	1	7	8	9	10	11	12	13	14	15	16	NA	
		0	1	NA	2	3	4	6	NA	7	NA	NA	NA	
			0	1	2	3	4	5	6	7	8	9	10	
			Low		Moderate		High							
			ATRIA Score											

[0089] Exemplary medical histories, such as stroke and bleed risk factors, for each of the 64 model patients, each falling within one of the 64 categories described above in Table 13 are shown below in Table 14.

Table 14.

Patient	sex	Hyp.	CHF	Diab.	Age	P.Stk/TIA	Anem.	Hist. Bld	Renal	CHADS ₂	ATRIA
1	1	0	0	0	74	0	0	0	0	0	0
2	1	0	0	0	74	0	0	0	1	0	2
3	1	0	0	0	74	0	1	0	0	0	3
4	1	0	0	0	74	0	0	1	1	0	4
5	1	0	0	0	74	0	1	0	1	0	5
6	1	0	0	0	74	0	1	1	1	0	7
7	1	0	1	0	74	0	0	0	0	1	0
8	1	1	0	0	74	0	0	0	0	1	1
9	1	0	1	0	74	0	0	0	1	1	2
10	1	0	1	0	74	0	1	0	1	1	3
11	1	0	0	0	74	0	1	0	0	1	4
12	1	1	0	0	74	0	0	1	1	1	5
13	1	1	0	0	74	0	1	1	0	1	6
14	1	0	0	1	74	0	1	1	1	1	7
15	1	1	0	0	74	0	1	1	1	1	8
16	1	0	0	0	75	0	1	1	1	1	9
17	1	0	1	1	74	0	0	0	0	2	0
18	1	1	1	0	74	0	0	0	0	2	1
19	1	0	1	1	74	0	0	0	1	2	2
20	1	0	1	1	74	0	1	0	0	2	3
21	1	0	1	1	74	0	0	1	1	2	4
22	1	1	1	0	74	0	0	1	1	2	5
23	1	1	0	0	74	0	1	1	0	2	6
24	1	0	1	1	74	0	1	1	1	2	7
25	1	1	1	0	74	0	1	1	1	2	8
26	1	0	1	0	75	0	1	1	1	2	9
27	1	1	0	0	75	0	1	1	1	2	10
28	1	0	1	0	74	1	0	0	0	3	0
29	1	1	1	1	74	0	0	0	0	3	1
30	1	0	1	1	75	0	0	0	0	3	2
31	1	1	1	1	74	0	0	0	1	3	3
32	1	0	1	1	75	0	0	0	1	3	4
33	1	1	1	1	74	0	0	1	1	3	5

Patient	sex	Hyp.	CHF	Diab.	Age	P.Stk/TIA	Anem.	Hist. Bld	Renal	CHADS ₂	ATRIA
34	1	0	1	1	75	0	0	1	1	3	6
35	1	1	0	0	75	0	0	1	1	3	7
36	1	1	1	0	75	0	1	0	1	3	8
37	1	0	1	1	75	0	1	1	1	3	9
38	1	1	1	0	75	0	1	1	1	3	10
39	1	0	1	1	74	1	0	0	0	4	0
40	1	1	0	1	74	1	0	0	0	4	1
41	1	0	1	0	75	1	0	0	0	4	2
42	1	0	1	1	74	1	1	0	1	4	3
43	1	0	0	1	75	1	0	0	1	4	4
44	1	0	1	0	75	1	1	0	0	4	5
45	1	0	1	0	75	1	0	1	1	4	6
46	1	0	1	0	75	1	1	1	0	4	7
47	1	1	0	0	75	1	1	1	0	4	8
48	1	0	1	0	75	1	1	1	1	4	9
49	1	1	0	0	75	1	1	1	1	4	10
50	1	1	1	1	74	1	0	0	1	5	1
51	1	0	1	1	75	1	0	0	0	5	2
52	1	1	0	1	75	1	0	0	0	5	3
53	1	0	1	1	75	1	0	1	0	5	4
54	1	0	1	1	75	1	1	0	0	5	5
55	1	1	0	1	75	1	1	0	0	5	6
56	1	0	1	1	75	1	1	1	0	5	7
57	1	1	0	1	75	1	1	1	0	5	8
58	1	0	1	1	75	1	1	1	1	5	9
59	1	1	0	1	75	1	1	1	1	5	10
60	1	1	1	1	75	1	0	0	0	6	3
61	1	1	1	1	75	1	0	0	1	6	5
62	1	1	1	1	75	1	0	1	1	6	7
63	1	1	1	1	75	1	1	0	1	6	8
64	1	1	1	1	75	1	1	1	1	6	10

Sex = sex of patient, where 1 = male.

CHR = heart failure

Diab. = Diabetes mellitus

P.Stk / TIA = prior stroke or TIA

Anem. = anemia

Hist. Bld. = history of any bleeding

Renal. = renal bleeding

[0090] To provide a treatment recommendation for the matrix shown above in Table 14, a second-order Monte Carlo simulation analysis may be conducted to sample each row of Table 14. For each patient (sample), a simulation analysis using expected value calculations may be performed to determine the QALYs for each treatment option. It should be noted that these 64 hypothetical patients do not represent the entire spectrum of possible risks. For example, age has a continuous effect on mortality and the ages assigned to this hypothetical cohort were selected nearest the cut-off threshold. In order to evaluate the impact that age has on the model recommendations, two additional hypothetical cohorts, one to represent 75 or older, using an average age of 82; and one to represent < 75, using an average age of 61, may also be used. These mean age groups may be chosen based on the mean age of these

respective groups that maybe observed in the Marketscan database. In restricting the age groups as mentioned above, the default cohort size may be reduced to 46 available cells in the 82 year old cohort, and 48 available cells in the 61 year old group.

[0091] The MarketScan database consists of more than 121 million patient records (commercial including employees, dependents, and retirees, Medicare supplement, Medicaid) that allow queries about patient-level payments, pharmacy, laboratory, and medical records data. This database may be representative of the U.S. general population covered by private health insurance.

EXAMPLE 5: EXEMPLARY MARKOV SIMULATION

[0092] In one exemplary embodiment, a Markov simulation may be used to compare the quality adjusted life expectancy (e.g., predicted QALYs) of patients under a selected anticoagulant treatment, such as warfarin or aspirin, given an individual patient's risk factors for stroke and bleeds. The exemplary simulation may be a discrete-time state transition model, using deterministic expected value calculations (e.g., "cohort" analysis) or any other suitable decision tree algorithms (e.g., Monte Carlo algorithm). The Markov simulation may comprise a computer-simulated model designed to sample medical history from a specific patient and generate a treatment recommendation. The patients may be any suitable patient suffering from atrial fibrillation or any patient in need of anticoagulant treatment. For example, the patients may be part of the Medstat Marketscan® AFIB cohort.

[0093] Figure 3 provides a generalized decision flow chart for an exemplary embodiment of the Markov simulation for quantifying a net benefit of a particular anticoagulant treatment option. The simulation first evaluates parameter variables for covariates, e.g., risk factors, that relate to the patient's risk for stroke and/or bleed. As shown in Figure 3, the simulation begins in step **30** with a need to determine which treatment option would be most suitable for a particular patient, such as, for example, whether a patient should receive warfarin, whether a patient should receive aspirin, and/or decision between administering to the patient warfarin or aspirin. Next, in step **32**, specific risk factors relating to a particular patient's risk for stroke and/or bleed events may be obtained by manual input by an operator using a user interface, obtained electronically from a computer-readable medium, electronically retrieved from a remote database via a communications network. The computer-readable medium and/or the database may comprise entries relating to the patient's

risk for stroke and/or bleed events, particularly the computer-readable medium and/or the database may comprise or store on said medium or database, the patient's electronic medical records (EMRs). Specific stroke risk factors may include, for example, prior stroke or transischemic attack (TIA), having an age greater than 75 years, hypertension, diabetes mellitus and heart failure. These stroke risk factors may be assigned a weighted score that is then correlated to empirically generated stroke rates (steps **34** and **36**). One suitable index for providing weighted scores to stroke risk factors and generating probabilities for stroke events is the CHADS₂ stroke-risk index described in Example 1 (step **34**). Specific bleed risk factors may include, for example, anemia, having an age greater than 75 years, history of any bleeding, an eGFR less than 30, and history of hypertension. These bleed risk factors may be assigned a weighted score that is then correlated to bleed rates, preferably empirically derived bleed rates. One particularly suitable index for providing weighted scores for bleed risk factors and generating probabilities for bleed events, is the ATRIA bleed-risk index described in Example 2, or the alternative risk-stratification scheme described in Example 3 (step **36**).

[0094] The stroke and bleed indices (e.g., CHADS₂ and ATRIA scores and probabilities) may be used to establish a baseline risk for stroke and bleed events, respectively. Patients enter stroke and/or hemorrhage conditions at rates that are defined by or correlated to this baseline risk profile. For example, the CHADS₂ scores and probabilities may be used to generate the baseline probabilities for a patient's risk for ischemic stroke **46**, which includes moderate and severe stroke **44**, as well as mild stroke **48**. A particular distribution for the severity of a stroke event, such as an ischemic stroke **46**, may relate to the particular treatment considered by the simulation. For example, warfarin may provide a smaller percentage of fatal ischemic strokes as compared to aspirin, whereas aspirin may reduce the percentage of fatal ischemic strokes as compared to no treatment.

[0095] The stroke rates predicted by a stroke index, such as, for example, the CHADS₂ scores and probabilities may be adjusted for the specific treatment option that is evaluated. For example, the stroke rates predicted by the patient's CHADS₂ scores may be adjusted for treatment with a specific treatment option, based on the relative risks of the treatment option as compared to the baseline predicted by the stroke index. For example, the CHADS₂ score is generated using data generated from patients under treatment with aspirin. In an exemplary embodiment, a patient having a CHADS₂ score of 3 may have a moderate risk for stroke events, at a stroke rate of 5.9 per 100 patient years. To adjust the probabilities

from the CHADS₂ index to predicted probabilities for other treatment options, such as administration of warfarin, an adjustment factor representing the relative risk of the baseline treatment as compared to the selected treatment may be applied. In particular, the relative risk for warfarin compared to aspirin is 0.48; therefore, a patient having a CHADS₂ score of 3 would have a stroke rate of $5.9 \times 0.48 = 2.832$ per 100 patient years. In addition, the stroke rates may be further adjusted to reflect an increased risk for stroke after the occurrence of a first stroke event. For example, for patients that have experienced a first stroke, the risk of a recurrent stroke may be twice of the baseline rate. These adjustment factors may be statistically derived from historic data or may be manually assigned by projecting the relative risks and/or benefits of the selected treatment option. Exemplary values for the relative risk of alternative treatment options, such as no treatment, or administration of warfarin, as compared to aspirin is provided below in Table 15. In addition, the relative risk of recurrent stroke is also provided below in Table 15.

Table 15.

Ischemic Stroke Parameters	Relative Risk
Relative Risk No Treatment vs. Aspirin	1.3
Relative Risk Warfarin vs. Aspirin	0.48
Relative Risk of Recurrent Stroke vs. Baseline Stroke Risk	2

[0096] In addition, if the patient suffers from a stroke, the severity of the stroke may breakdown differently depending on the treatment option. For example, a patient having a CHADS₂ score of 3 under going warfarin treatment, may have a risk of $2.832 \times 8.2\% = 0.23224$ per 100 patient years for a fatal stroke and a risk of $2.832 \times 40.2\% = 1.138464$ per 100 patient years for a moderate or severe stroke. Exemplary distributions of the severity of stroke under treatment with warfarin, treatment with aspirin, or no treatment is provided below in Table 16.

Table 16.

Treatment Option	Severity of Stroke	Percentage of Total Ischemic Stroke
Warfarin	Fatal	8.2%
	Moderate / Severe	40.2%
	Mild	42.5%

	Reversible	9.1%
Aspirin	Fatal	17.9%
	Moderate / Severe	30.0%
	Mild	41.0%
	Reversible	11.0%
No Treatment	Fatal	22.3%
	Moderate / Severe	37.1%
	Mild	32.0%
	Reversible	8.6%

[0097] Additionally, baseline hemorrhage conditions may be predicted by ATRIA scores and probabilities, such as those described in Examples 2 and 3 (step 36). The ATRIA scores predict the probabilities for a bleed event, including for example, intracranial hemorrhage (ICH) 38, a major extra-cranial hemorrhage (ECH) 40, or a minor bleed 42. The severity of the bleeds may also depend on the particular treatment option. In particular, patients taking warfarin may have a higher risk for a major bleed event such as ICH and/or ECH than patients taking aspirin or receiving no treatment at all.

[0098] The bleed rate predicted by a bleed index, such as, for example the ATRIA scores and probabilities, may be adjusted for the specific treatment option that is evaluated. For example, the bleed rates predicted by the patient's ATRIA scores may be adjusted for treatment with a specific treatment option, based on the relative risks of the treatment option as compared to the baseline predicted by the bleed index. In particular the probabilities may be adjusted to reflect the bleed risk rates for aspirin, as well as no treatment. For example, the ATRIA score is generated using data obtained from patients under treatment with warfarin. In an exemplary embodiment using the alternative ATRIA model described in Example 3, a patient having an ATRIA score of 7 may have a high risk for bleed events, at a bleed rate of 6.231 per 100 patient years for major bleeds with under treatment with warfarin. Since the ATRIA score provides a single rate for major bleeds, the rate for the different types of bleed events may be statistically derived from historic data or may be manually assigned by projecting the relative risks and/or benefits of the selected treatment option. For example, if the patient suffers from a bleed event, the severity of the bleed may breakdown differently depending on the treatment option. In particular, the rate of ICH% / year under warfarin is 0.25 and the rate of major non-cranial bleed % / year under warfarin is 2.22. Therefore, a patient having an ATRIA score of 7 would have a rate for ICH under warfarin of $6.231 \times (0.25 / 0.25 + 2.22) = 0.630668$ per 100 patient years.

[0099] Exemplary distributions of the severity of bleed events under treatment with warfarin are provided below in Table 17. The ICH, Major ECH, and Minor Bleed rates shown in Table 17 are used to determine proportion of bleed type, respectively. In the particular exemplary distributions provided in Table 12, the probabilities for each of these events may be derived from statistical analysis of empirical data, retrieved from published literature and/or manually assigned based on the knowledge of one skilled in the art, such as mortality rates following major bleeds and INR values within the normal range.

Table 17.

Bleed Parameters	Probability
Rate of ICH % / year Warfarin	0.25
% of ICH that are Fatal on warfarin	0.516
% of ICH that are Fatal NOT on warfarin	25.9%
Rate of Major Non-cranial Bleed % / year Warfarin	2.22
% of ECH that are Fatal	1.5%
% of ECH that are GI	89.9%
% drug discontinuation rate following non-fatal ECH	25.0%
Rate of Minor Bleed % / year Warfarin	11.80

[0100] To adjust the probabilities from the ATRIA index to predict probabilities for treatment options other than warfarin, such as administration of aspirin, an adjustment factor representing the relative risk of the baseline treatment (i.e., warfarin) as compared to the selected treatment may be applied. In particular, the relative risk for aspirin vs. warfarin, is 0.64. Therefore, a patient having an ATRIA score of 7 (as calculated using the alternative ATRIA index of Example 3) would have a rate for ICH under aspirin of $0.630668 \times 0.64 = 0.403628$ per 100 patient years. In addition, the bleed rates may be further adjusted to reflect an increased risk for bleed events after the occurrence of a first bleed event. For example, for patients that have experienced a first bleed event, the risk of a recurrent bleed may be 1.5 times of the baseline rate. Exemplary values for the relative risk of alternative treatment options, such as no treatment, or administration of aspirin, as compared to warfarin is provided below in Table 18. In addition, the relative risk of recurrent bleed is also provided below in Table 18.

Table 18.

Bleed Parameters	Relative Risk
Relative Risk of ICH BLEED with aspirin vs. warfarin	0.64
Relative Risk of ICH BLEED No Treatment vs. warfarin	0.44
Relative Risk of Major ECH BLEED No Treatment vs. warfarin	0.42
Relative Risk of Major ECH BLEED with aspirin vs. warfarin	0.5
Relative risk of recurrent bleed versus baseline bleed risk	1.5

[0101] Each iteration of the simulation may be further discounted to reflect the probability that a patient may die from an adverse event unrelated to stroke and/or bleed events. For example, each iteration may be discounted at a rate of at least 1%, at least 2%, at least 3%, at least 5% and at least 10% to reflect the probability that a patient may die from an adverse event unrelated to stroke and/or bleed events. Suitable rates may be obtained from the U.S. Vital Statistics Data based on the age and sex of the patient.

[0102] Non-disease specific (demographic-based) mortality rates, adjusted for age and sex may also be used to adjust the predicted probability of death for a particular patient. Additional adjustments may be applied to account for the relative risk of dying from other causes specific to patients with nonvalvular atrial fibrillation (NVAF), with or without prior stroke. Exemplary rates for such adjustments for patients on aspirin are shown in Table 19 below. The adjustments for other treatment options may be obtained using an additional adjustment factor for the relative risk of death by other events of other treatment options vs. aspirin. For example, an additional adjustment factor for the relative risk of warfarin vs. aspirin may be 0, and therefore, the relative risk of warfarin for the risk of dying from other causes would be the same as that of aspirin. In addition, relative risks of death from recurrent bleeds and stroke are also provided in Table 19.

Table 19.

Mortality Parameters	Relative Risk
Relative Risk of non-stroke, non-bleed death With NVAf (with Aspirin)	1.3
Relative Risk of non-stroke, non-bleed death With NVAf and Prior Stroke (with Aspirin)	2.3
Relative Risk of Death from Recurrent Disabling Bleed vs. Baseline	1.5
Relative Risk of Death from Recurrent Disabling Stroke vs. Baseline	1.5

[0103] In some embodiments, the simulation assumes that the relative risk of dying from other causes is the same for patients on aspirin and patients receiving no treatment. Additionally, the simulation may also assume that patients with prior ICH would have the same relative risk of dying from other causes as those with prior stroke.

[0104] Some of the stroke and/or bleed conditions predicted by the model may result in the patient suffering from transient and/or permanent morbidity **50**. Under certain conditions, a patient's quality of life may be adjusted or diminished **54** for any period of time that he or she remains in conditions that result in transient and/or permanent morbidity. For example, a patient who has suffered from a major stroke or an intra-cranial hemorrhage may have a significantly reduced quality of life as a result of the severity and long term morbidity associated with these conditions.

[0105] The Markov simulation may iterate over a distinct time line in a recursive manner to predict a patient's life expectancy **52** under a particular treatment option. Moreover, for each iteration, the simulations generate probabilities for ischemic stroke **46** and the probabilities for various bleed events, including ICH **38**, Major ECH **40**, and minor bleeds **42**. In addition, for each iteration, the patient's risk for stroke, hemorrhage, and mortality associated with these events may be adjusted to reflect the modified predicted risks of the patient during each iteration or expected period of life predicted by the simulation. As the simulation iterates over a distinct time line, the patient's event and mortality risk may also be adjusted for the predicted aging of the patient. Based on the overall benefit in life expectancy predicted using the recursive methods of the Markov simulation **52**, reduced by any reductions in quality of life **54** resulting from stroke and/or bleed conditions or from limitations to a patient's lifestyle under a particular treatment option, for example, limitation

in diet under warfarin treatment, a treatment recommendation **56** may be provided based on the net benefit of any particular treatment option or combination of treatment options.

EXAMPLE 6: EXEMPLARY HEALTH STATES FOR MARKOV SIMULATION

[0106] In an exemplary embodiment shown in Figure 4, for each treatment option **90**, the simulation may comprise a plurality of health states that may comprise information, variables and/or data that represent the condition of the patient, and the course of treatment that the patient is predicted to undergo within each expected period of life predicted by the simulation. The condition of the patient may include, for example, lack of adverse events, death, recurrent and non-recurrent stroke events, recurrent and non-recurrent bleed events, and combinations of stroke events and bleed events. Exemplary embodiments of stroke events include, no ischemic stroke, moderate to severe ischemic stroke, mild ischemic stroke, reversible ischemic stroke, reversible ischemic stroke, and fatal ischemic stroke. Examples of suitable bleed events include, no bleeds, intracranial hemorrhage or bleed, major non-cranial hemorrhage or bleed, minor hemorrhage or bleed, prior major non-cranial hemorrhage or bleed, and fatal hemorrhage or bleed. The course of treatment may encompass include, for example, administration of said treatment option at one or more different dosages, temporary discontinuation of the selected treatment option, and permanent discontinuation of the selected treatment option.

[0107] In one particular embodiment, the simulation may encompass 31 different health states for each treatment option, which are summarized below in Table 20.

Table 20.

<i>Health State</i>	<i>Patient's Condition</i>		<i>Course of Treatment</i>
	<i>Stroke Events</i>	<i>Bleed Events</i>	
1	None	None	ON
2	None	None	OFF
3	Moderate to Severe Ischemic Stroke	-----	ON
4	Mild Ischemic Stroke	-----	ON
5	Reversible Ischemic Stroke	-----	ON
6	Recurrent Stroke	-----	ON
7	-----	Intra Cranial Hemorrhage	Permanently Discontinue
8	-----	Major Non-Cranial Hemorrhage	Temporarily Discontinue
9	-----	Major Non-Cranial	ON

<i>Health State</i>	<i>Patient's Condition</i>		<i>Course of Treatment</i>
	<i>Stroke Events</i>	<i>Bleed Events</i>	
		Hemorrhage	
10	-----	Major Non-Cranial Hemorrhage	Permanently Discontinue
11	-----	Recurrent Bleed	Permanently Discontinue
12	Perm. Stroke	Intra Cranial Hemorrhage	Permanently Discontinue
13	Reversible Ischemic Stroke	Intra Cranial Hemorrhage	Permanently Discontinue
14	Moderate to Severe Ischemic Stroke	Major Non-Cranial Hemorrhage	Temporarily Discontinue
15	Moderate to Severe Ischemic Stroke	Prior Major Non-Cranial Hemorrhage	ON
16	Moderate to Severe Ischemic Stroke	Major Non-Cranial Hemorrhage	Permanently Discontinue
17	Mild Ischemic Stroke	Major Non-Cranial Hemorrhage	Temporarily Discontinue
18	Mild Ischemic Stroke	Prior Major Non-Cranial Hemorrhage	ON
19	Mild Ischemic Stroke	Major Non-Cranial Hemorrhage	Permanently Discontinue
20	Recurrent Stroke	Prior Major Non-Cranial Hemorrhage	ON
21	Recurrent Stroke	Major Non-Cranial Hemorrhage	Temporarily Discontinue
22	Recurrent Stroke	Major Non-Cranial Hemorrhage	Permanently Discontinue
23	Reversible Ischemic Stroke	Major Non-Cranial Hemorrhage	ON
24	Reversible Ischemic Stroke	Major Non-Cranial Hemorrhage	Temporarily Discontinue
25	Reversible Ischemic Stroke	Major Non-Cranial Hemorrhage	Permanently Discontinue
26	Prior Reversible Ischemic Stroke	-----	ON
27	-----	Prior Major Non-Cranial Hemorrhage	ON
28	-----	Prior Major Non-Cranial Hemorrhage	Permanently Discontinue
29	Prior Reversible Ischemic Stroke	Prior Major Non-Cranial Hemorrhage	ON
30	Prior Reversible Ischemic Stroke	Prior Major Non-Cranial Hemorrhage	Permanently Discontinue
31	DEAD		

[0108] The 31 different health states listed in Table 20 provide for means to account for recurrent bleed and stroke states, various combinations of stroke and bleed events, as well as state of drug discontinuation for each treatment option **90** simulated. Figure 2 provides a tree diagram demonstrating the basic structure of the simulation and the available health states that may be predicted by the simulation. In particular, Figure 2 shows the different health states available at the start of the simulation. For each iteration of the simulation, the patient may be subject to risks of thromboembolism, hemorrhage or death based on specific risk factors unique to the patient. In an exemplary embodiment, patients entered into the Markov simulations starts in a “well” state with atrial fibrillation and transitioned along decision path ways to one of the following mutually exclusive health states: well state with AF, transient ischemic attack (TIA), stroke without permanent disability, mild stroke, or moderate/severe stroke with permanent morbidity, intracranial hemorrhage, extracranial major hemorrhage, minor hemorrhage, or death. For example, the patient may experience a fatal or non-fatal stroke, a fatal or non-fatal bleed or die of other unrelated cause during each iteration of the simulation. The simulation may iterate over any period of time, preferably a fixed period of time. For example, the simulation may iterate every month, every 3 months, every 6 month, every 9 months, every year, every 10 days, every 30 days, every 60 days, every 90 days, or every 120 days. Preferably, the simulation iterates every 90 days, because patients are unlikely to experience more than one adverse event within this time frame. Moreover, this time frame also correlates to a typical period of temporary drug discontinuation following an extracranial hemorrhage (ECH). For each iteration, if the patient experiences an adverse event, he or she transitions to a subsequent health state corresponding to the adverse event at the start of the next cycle. The subsequent health state may also be derived from the existing condition of the patient and the existing course of treatment.

[0109] The patient’s course of treatment may be adjusted following specific adverse events. For example, patients that start on warfarin and experience an ICH may be taken off treatment permanently. As another example, patients that experience a major ECH follow one of three possible pathways relating to drug treatment: (1) for patients receiving warfarin, approximately 25% may discontinue treatment permanently; (2) of the remaining patients receiving warfarin, 89% may temporarily discontinue treatment for a period of 3 months or 90 days, and (3) 11% remain on treatment continuously. In a contrary example, patients starting on Aspirin that experience a stroke may subsequently be switched to warfarin.

Additionally, discontinuation rates for a particular treatment may also be adjusted based on non-clinical events, to reflect the burden to the patient under certain treatment options, such as adhering to restrictions that are associated with the administration of warfarin. Such adjustments for non-clinical events, may occur in the presence or in the absence of any adverse event.

[0110] Some events such as major strokes and ICH may cause permanent disability. Other events such as major non-cranial bleeds or reversible strokes cause temporary disabilities. For the each period of life predicted by the simulation, an amount of quality adjusted life years (QALY) may be accrued. For example, a patient having a full year of life predicted by the simulation with full-health, the patient may accrue a QALY of 1. Death may be represented by a QALY of 0. For example, each iteration that occurs every 3 months or 90 days, a QALY of 0 to approximately 0.25 may be accrued. The QALY rates for adverse events may be categorized into those carrying long-term morbidity or disability and short-term or transient morbidity or disability. Patients predicted to suffer from permanent disabilities would remain at a diminished state of health ($\text{QALY} < 1$) for the remaining duration of their life predicted by the simulation. Patients predicted to suffer from temporary disabilities may return to their baseline health status after leaving a non-permanent disability state. Drug treatment, probability of future events, and mortality rates may be adjusted with each iteration. For example, following a non-fatal intracranial hemorrhage, a patient may be discontinued from warfarin, the probability of a subsequent bleed may be increased, and the probability of death from the subsequent bleed may also be increased.

[0111] Because warfarin and aspirin therapy requires routine monitoring and/or certain lifestyle modifications, patients receiving warfarin and aspirin would have a lower quality of life and assigned a lower QALY value than patients who did not receive stroke prophylaxis pharmacotherapy. In particular, patients that are well and on warfarin may accrue a slightly lower QALY than those on aspirin for each period of predicted life in view of the compliance burden for warfarin administration on the patient. Additionally, for warfarin patients, quality of life may be diminished to a slightly greater extent for the first cycle of the model to represent the added burden of initiation of warfarin treatment. Minor bleeds may carry the same reduction in QALY as other short-term disabilities. However, the simulation may apply this reduction for only 2 days, as opposed to a full iteration or the remaining duration that the patient experiences the disability. Exemplary values of the

QALY benefits as a function of the patient's condition and life style under the treatment are provided below in Table 21.

Table 21.

Quality of Life Parameters	Annual QALY
<i>Healthy</i>	
Warfarin	0.987
Aspirin	0.998
Initiation of Warfarin Therapy	0.98
Well and off treatment	1
<i>Long Term Morbidity</i>	
Moderate or Severe Stroke or ICH	0.39
Mild Stroke	0.75
<i>Short Term Morbidity</i>	
Major Non-Cranial Bleed or Reversible Stroke	0.8
Minor Bleed	0.8
Reversible Stroke	0.8 (this discounted QALY is only applied for 2 days)
Minor Bleed Transition Reward Disutility	0.0010959
DEAD	0

[0112] In addition, the Framingham Risk equation described by Sorensen et al., “Cost-effectiveness of warfarin: Trial versus ‘real-world’ stroke prevention in atrial fibrillation,” American Heart Journal, Vol. 157, No. 6, 1064-73 (2009) may be used to adjust stroke risk based on age. For example, the risk of stroke may increase by a factor of 1.8 for each decade of life. Similarly, bleed risks increase with age, but at a slower rate. For example, an analogous may be an increase of 1.3 for each decade of life.

[0113] Each branch of the Markov simulation may terminate when it reaches Health State 31, death (step 3100). Alternatively, the simulation may halt when at least 90%, at least 95%, at least 97%, at least 98%, at least 99% or at least 99.9% of a computer simulated cohort reaches Health State 31, death. Preferably, the simulation terminates when approximately 99.9% of the computer simulated cohort is dead. Alternatively, the Markov simulation may be used to simulate any length of time, such as, for example a period of 90 days, 180 days, 3 month, 6 months or 1 year.

Health State 1 (step 100)

[0114] In an exemplary embodiment of the present invention, although the simulation may begin at any suitable health state, the simulation typically starts at Health State 1 (step **100**), where the patient's condition is well or lack of an adverse stroke or bleed event (except for atrial fibrillation) and under a course of treatment that comprises administration of a particular treatment option to the patient. For each iteration of the simulation, there is a predicted probability that the patient may die from adverse events unrelated to stroke and/or bleed events **102**. In some embodiments, the predicted probability that the patient may die from adverse events unrelated to stroke and/or bleed events may be obtained from the U.S. Vital Statistics Data based on the age and sex of the patient and adjusted to reflect the relative risk of death not caused by stroke or bleed events for a patient in NVAF under a particular treatment option (e.g., 1.3 for aspirin and 1.3 for warfarin). In the embodiments, the predicted probability may be based on a baseline risk initially obtained from the U.S. Vital Statistics Data based on the age and sex of the patient that is further adjusted to reflect the relative risk of death by non-stroke or non-bleed events for increases in age predicted by the simulation. If the patient suffers from an adverse events unrelated to stroke and/or bleed events, a subsequent health state corresponding to this event would be Health State 31, death **3100**.

[0115] The patient may also experience stroke events **104**, bleed events **106**, or no adverse events **108**. The probability of the patient experiencing stroke events **104** may be determined using the baseline risk profile generated by a stroke index, such as, for example, the CHADS₂ scores and probabilities, which may be adjusted by the relative risk for the selected treatment option as compared to aspirin. If the patient is predicted to suffer from a stroke event **104**, the patient may experience a fatal event **110**, a moderate to severe ischemic stroke **112**, a mild ischemic stroke **114**, or a reversible ischemic stroke **116**. The probabilities of each of these stroke events may depend on the distribution of the severity of stroke events for the selected treatment option. For example, for a patient receiving warfarin, 8.2% of the stroke events are predicted to result in a fatal event **110**, 40.2% of the stroke events are predicted to result in moderate to severe ischemic stroke **112**, 42.5% of the stroke events are predicted to result in mild ischemic stroke **114**, and 9.1% of the stroke events are predicted to result in reversible ischemic stroke **116**. If the patient is predicted to suffer from a fatal event **110**, a subsequent health state corresponding to this event would be Health State 31, death **3100**. If the patient is predicted to suffer from moderate to severe ischemic stroke **112**, a subsequent health state corresponding to this event would be Health State 3 (step **300**). If the

patient is predicted to suffer from mild ischemic stroke **114**, a subsequent health state corresponding to this event would be Health State 4 (step **400**). If the patient is predicted to suffer from reversible ischemic stroke **116**, a subsequent health state corresponding to this event would be Health State 5 (step **500**).

[0116] The probability of the patient experiencing bleed events **106** may be determined using the baseline risk profile generated by a bleed index, such as, for example, the ATRIA scores and probabilities, which may be adjusted by the relative risk for the selected treatment option as compared to warfarin. If the patient is predicted to suffer from a bleed event **106**, the patient may experience a fatal event **118**, intra-cranial hemorrhage **120**, major non-cranial hemorrhage, or minor hemorrhage **124**. The probabilities of each of these bleed events may depend on the distribution of the severity of bleed events for the selected treatment option. If the patient is predicted to suffer from a fatal event **118**, a subsequent health state corresponding to this event would be Health State 31, death **3100**. If the patient is predicted to suffer from intra-cranial hemorrhage **120**, a subsequent health state corresponding to this event would be Health State 7 (step **700**).

[0117] If the patient is predicted to suffer from a major non-cranial hemorrhage **122**, the simulation may predict that the patient could be permanently discontinued from the existing course of treatment **126**, which is the administration of the selected treatment option, and a subsequent health state corresponding to the bleed event and the new course of treatment would be Health State 10 (step **1000**). The patient may be permanently discontinued from the existing course of treatment **126** at any rate. Preferably, the patient may be permanently discontinued from the existing course of treatment **126** at a probability of 25%. Alternatively, the patient may remain under the selected treatment option **128**, but may be temporarily discontinued from the existing course of treatment **130** by a period of three months or 90 days. The patient may be temporarily discontinued from the existing course of treatment **130** at any rate. Preferably, the patient may be temporarily discontinued from the existing course of treatment **130** when the major non-cranial hemorrhage are gastrointestinal, which may, for example, be at a probability of 89.9%. If the patient is predicted to suffer from a major non-cranial hemorrhage **122** and the simulation predicts that the patient is temporarily discontinued from the existing course of treatment **130**, a subsequent health state corresponding to the bleed event and the new course of treatment would be Health State 8 (step **800**). If the patient is predicted to suffer from a major non-

cranial hemorrhage **122** and the simulation predicts that the patient continues the existing course of treatment **132**, a subsequent health state corresponding to the bleed event and the new course of treatment would be Health State 9 (step **900**).

[0118] If the patient is predicted to suffer from a minor hemorrhage **124**, the simulation may predict that the patient could be discontinued from the existing course of treatment **134**, and a subsequent health state corresponding to the bleed event and the new course of treatment would be Health State 2 (step **200**). If the patient is predicted to suffer from a minor hemorrhage **124**, the simulation may predict that the patient would continue the existing course of treatment **136**, and a subsequent health state would remain as Health State 1 (step **100**). The patient may be discontinued from the existing course of treatment **134** and/or continue the selected treatment option **136** at any rate. Moreover, the probability of continuing a treatment option following a minor bleed **136** may be lower for warfarin than for other treatment options. For example, the probability of continuing warfarin following a minor bleed may be 60% per year, where as the probability of continuing other treatment options (e.g., aspirin, or edoxaban) may be 95% per year.

[0119] If the patient is predicted not to experience an adverse event **108**, the simulation may predict that the patient may be adherent and continue the existing course of treatment **140** or non-adherent and discontinue the existing course of treatment **138**. If the patient is adherent **140**, then the subsequent health state would remain as Health State 1 (step **100**). If the patient is non-adherent **138**, then the subsequent health state would be Health State 2 (step **200**) to reflect the condition of the patient and the new course of treatment. The patient's adherence and non-adherence to the existing course of treatment may be at any rate. Moreover, the probability of continuing a treatment option **140** may be lower for warfarin than for other treatment options. For example, the probability of continuing warfarin may be 60% per year, where as the probability of continuing other treatment options (e.g., aspirin, or edoxaban) may be 95% per year. The probabilities applied to the simulation may be adjusted based on the period of life predicted by an iteration of the simulation.

Health State 2 (step **200**)

[0120] In Health State 2 (step **200**), the patient's condition is well or lack of an adverse stroke or bleed event (except for atrial fibrillation) and is not being administered any particular treatment option. For each iteration of the simulation, there is a predicted

probability that the patient may die from adverse events unrelated to stroke and/or bleed events **202**, which includes adjustments to reflect the relative risk of death not caused by stroke or bleed events for a patient in NVAf under a particular treatment option (e.g., 1.3 for aspirin and 1.3 for warfarin). If the patient suffers from an adverse events unrelated to stroke and/or bleed events, a subsequent health state corresponding to this event would be Health State 31, death **3100**.

[0121] The patient may also experience stroke events **204**, bleed events **206**, or no adverse events **208**. The probability of the patient experiencing stroke events **204** may be determined using the baseline risk profile generated by a stroke index, such as, for example, the CHADS₂ scores and probabilities, which may be adjusted by the relative risk for the selected treatment option as compared to aspirin. If the patient is predicted to suffer from a stroke event **204**, the patient may experience a fatal event **210**, a moderate to severe ischemic stroke **212**, a mild ischemic stroke **214**, or a reversible ischemic stroke **216**. The probabilities of each of these stroke events may depend on the distribution of the severity of stroke events for the selected treatment option. If the patient is predicted to suffer from a fatal event **210**, a subsequent health state corresponding to this event would be Health State 31, death **3100**. If the patient is predicted to suffer from moderate to severe ischemic stroke **212**, a subsequent health state corresponding to this event would be Health State 3 (step **300**). If the patient is predicted to suffer from mild ischemic stroke **214**, a subsequent health state corresponding to this event would be Health State 4 (step **400**). If the patient is predicted to suffer from reversible ischemic stroke **216**, a subsequent health state corresponding to this event would be Health State 5 (step **500**).

[0122] The probability of the patient experiencing bleed events **206** may be determined using the baseline risk profile generated by a bleed index, such as, for example, the ATRIA scores and probabilities, which may be adjusted by the relative risk for the selected treatment option as compared to warfarin. If the patient is predicted to suffer from a bleed event **206**, the patient may experience a fatal event **218**, intra-cranial hemorrhage **220**, major non-cranial hemorrhage **222**, or minor hemorrhage **224**. The probabilities of each of these bleed events may depend on the distribution of the severity of bleed events for the selected treatment option. If the patient is predicted to suffer from a fatal event **218**, a subsequent health state corresponding to this event would be Health State 31, death **3100**. If

the patient is predicted to suffer from intra-cranial hemorrhage **220**, a subsequent health state corresponding to this event would be Health State 7 (step **700**).

[0123] If the patient is predicted to suffer from a major non-cranial hemorrhage **222**, the simulation may predict that the patient could be permanently discontinued from the treatment option **226** (e.g., administration of warfarin or aspirin), and a subsequent health state corresponding to the bleed event would be Health State 10 (step **1000**). The patient may be permanently discontinued from the treatment option **226** at any rate. Preferably, the patient may be permanently discontinued from the treatment option **226** at a probability of 25%. Alternatively, the patient may remain under the selected treatment option **128**, but may be temporarily discontinued **230** by a period of three months or 90 days. The patient may be temporarily discontinued **230** at any rate. Preferably, the patient may be temporarily discontinued from the existing course of treatment **230** when the major non-cranial hemorrhage are gastrointestinal, which may, for example, be at a probability of 89.9%. If the patient is predicted to suffer from a major non-cranial hemorrhage **222** and the simulation predicts that the patient is temporarily discontinued from the existing course of treatment **230**, a subsequent health state corresponding to the bleed event and the new course of treatment would be Health State 8 (step **800**). If the patient is predicted to suffer from a major non-cranial hemorrhage **222** and the simulation predicts that the patient continues the existing course of treatment **232**, a subsequent health state corresponding to the bleed event and the new course of treatment would be also be Health State 8 (step **800**), because the existing course of treatment does not administer any particular treatment option to the patient.

[0124] If the patient is predicted to suffer from a minor hemorrhage **224**, a subsequent health state would remain as Health State 2 (step **200**). Similarly, if the patient is predicted not to experience an adverse event **208**, the simulation may predict that a subsequent health state would also remain as Health State 2 (step **200**).

Health State 3 (step **300**)

[0125] In Health State 3 (step **300**), the patient is predicted to have moderate to severe ischemic stroke and under a course of treatment that comprises administration of a particular treatment option to the patient. In this particular health state, the patient is not predicted to suffer from an adverse bleed event. For each iteration of the simulation, there is a predicted probability that the patient may die from adverse events unrelated to stroke and/or bleed

events **302**, which includes adjustments to reflect an increased likelihood of death by other causes following a stroke, as well as the relative risk of death not caused by stroke or bleed events for a patient in NVAf under a particular treatment option (e.g., 1.3 for aspirin and 1.3 for warfarin). An exemplary increase of the relative risk of death by adverse events unrelated to stroke and/or bleed event after a patient suffers from a stroke may be 2.3. If the patient suffers from an adverse events unrelated to stroke and/or bleed events, a subsequent health state corresponding to this event would be Health State 31, death **3100**.

[0126] The patient may also experience stroke events **304**, bleed events **306**, or no adverse events **308**. The probability of the patient experiencing stroke events **304** may be determined using the baseline risk profile generated by a stroke index, such as, for example, the CHADS₂ scores and probabilities, which may be adjusted by the increase in relative risk of recurrent strokes and the relative risk for the selected treatment option as compared to aspirin. The relative risk of recurrent stroke may, for example, be at a rate of 2. If the patient is predicted to suffer from a stroke event **304**, the patient may experience a fatal event **310** or a moderate to severe ischemic stroke **312**. The probabilities of each of these stroke events may depend on the distribution of the severity of stroke events for the selected treatment option. For example, for a patient receiving warfarin, 8.2% of the stroke events are predicted to result in a fatal event **310**, the remainder of the stroke events is predicted to result in moderate to severe ischemic stroke **312**. If the patient is predicted to suffer from a fatal event **310**, a subsequent health state corresponding to this event would be Health State 31, death **3100**. If the patient is predicted to suffer from moderate to severe ischemic stroke **312**, a subsequent health state corresponding to this event would be Health State 6 (step **600**), which reflects the patient having suffered from a recurrent stroke, after having already experienced a moderate to severe ischemic stroke, which is the existing condition represented by Health State 3 (step **300**).

[0127] The probability of the patient experiencing bleed events **306** may be determined using the baseline risk profile generated by a bleed index, such as, for example, the ATRIA scores and probabilities, which may be adjusted by the relative risk for the selected treatment option as compared to warfarin. If the patient is predicted to suffer from a bleed event **306**, the patient may experience a fatal event **314**, intra-cranial hemorrhage **316**, major non-cranial hemorrhage **318**, or minor hemorrhage **320**. The probabilities of each of these bleed events may depend on the distribution of the severity of bleed events for the

selected treatment option. If the patient is predicted to suffer from a fatal event **314**, a subsequent health state corresponding to this event would be Health State 31, death **3100**. If the patient is predicted to suffer from intra-cranial hemorrhage **316**, a subsequent health state corresponding to this event would be Health State 12 (step **1200**).

[0128] If the patient is predicted to suffer from a major non-cranial hemorrhage **318**, the simulation may predict that the patient could be permanently discontinued from the existing course of treatment **322**, which is the administration of the selected treatment option, and a subsequent health state corresponding to the bleed event and the new course of treatment would be Health State 10 (step **1000**). The patient may be permanently discontinued from the existing course of treatment **322** at any rate. Preferably, the patient may be permanently discontinued from the existing course of treatment **322** at a probability of 25%. Alternatively, the patient may remain under the selected treatment option **324**, but may be temporarily discontinued from the existing course of treatment **326** by a period of three months or 90 days. The patient may be temporarily discontinued from the existing course of treatment **326** at any rate. Preferably, the patient may be temporarily discontinued from the existing course of treatment **326** when the major non-cranial hemorrhage are gastrointestinal, which may, for example, be at a probability of 89.9%. If the patient is predicted to suffer from a major non-cranial hemorrhage **318** and the simulation predicts that the patient is temporarily discontinued from the existing course of treatment **326**, a subsequent health state corresponding to the bleed event and the new course of treatment would be Health State 14 (step **1400**). If the patient is predicted to suffer from a major non-cranial hemorrhage **318** and the simulation predicts that the patient continues the existing course of treatment **328**, a subsequent health state corresponding to the bleed event and the new course of treatment would be Health State 15 (step **1500**).

[0129] If the patient is predicted to suffer from a minor hemorrhage **320**, a subsequent health state would remain as Health State 3 (step **300**). Similarly, if the patient is predicted not to experience an adverse event **308**, the simulation may predict that a subsequent health state would also remain as Health State 3 (step **300**).

Health State 4 (step 400)

[0130] In Health State 4 (step **400**), the patient is predicted to have mild ischemic stroke and under a course of treatment that comprises administration of a particular treatment

option to the patient. In this particular health state, the patient is not predicted to suffer from an adverse bleed event. For each iteration of the simulation, there is a predicted probability that the patient may die from adverse events unrelated to stroke and/or bleed events **402**, which includes adjustments to reflect an increased likelihood of death by other causes following a stroke, as well as the relative risk of death not caused by stroke or bleed events for a patient in NVAf under a particular treatment option (e.g., 1.3 for aspirin and 1.3 for warfarin). An exemplary increase of the relative risk of death by adverse events unrelated to stroke and/or bleed event after a patient suffers from a stroke may be 2.3. If the patient suffers from an adverse events unrelated to stroke and/or bleed events, a subsequent health state corresponding to this event would be Health State 31, death **3100**.

[0131] The patient may also experience stroke events **404**, bleed events **406**, or no adverse events **408**. The probability of the patient experiencing stroke events **404** may be determined using the baseline risk profile generated by a stroke index, such as, for example, the CHADS₂ scores and probabilities, which may be adjusted by the increase in relative risk of recurrent strokes and the relative risk for the selected treatment option as compared to aspirin. The relative risk of recurrent stroke may, for example, be at a rate of 2. If the patient is predicted to suffer from a stroke event **404**, the patient may experience a fatal event **410**, a moderate to severe ischemic stroke **412**, or a mild ischemic stroke **414**. The probabilities of each of these stroke events may depend on the distribution of the severity of stroke events for the selected treatment option. For example, for a patient receiving warfarin, 8.2% of the stroke events are predicted to result in a fatal event **410**, 40.2% of the stroke events are predicted to result in moderate to severe ischemic stroke **412**, and the remainder of the stroke events is predicted to result in mild ischemic stroke **414**. If the patient is predicted to suffer from a fatal event **410**, a subsequent health state corresponding to this event would be Health State 31, death **3100**. If the patient is predicted to suffer from moderate to severe ischemic stroke **412**, a subsequent health state corresponding to this event would be Health State 6 (step **600**). If the patient is predicted to suffer from mild ischemic stroke **414**, a subsequent health state corresponding to this event would be Health State 6 (step **600**), after having already experienced a mild ischemic stroke, which is the existing condition represented by Health State 4 (step **400**).

[0132] The probability of the patient experiencing bleed events **406** may be determined using the baseline risk profile generated by a bleed index, such as, for example,

the ATRIA scores and probabilities, which may be adjusted by the relative risk for the selected treatment option as compared to warfarin. If the patient is predicted to suffer from a bleed event **406**, the patient may experience a fatal event **416**, intra-cranial hemorrhage **418**, major non-cranial hemorrhage **420**, or minor hemorrhage **422**. The probabilities of each of these bleed events may depend on the distribution of the severity of bleed events for the selected treatment option. If the patient is predicted to suffer from a fatal event **416**, a subsequent health state corresponding to this event would be Health State 31, death **3100**. If the patient is predicted to suffer from intra-cranial hemorrhage **418**, a subsequent health state corresponding to this event would be Health State 12 (step **1200**).

[0133] If the patient is predicted to suffer from a major non-cranial hemorrhage **420**, the simulation may predict that the patient could be permanently discontinued from the existing course of treatment **424**, which is the administration of the selected treatment option, and a subsequent health state corresponding to the bleed event and the new course of treatment would be Health State 19 (step **1900**). The patient may be permanently discontinued from the existing course of treatment **424** at any rate. Preferably, the patient may be permanently discontinued from the existing course of treatment **424** at a probability of 25%. Alternatively, the patient may remain under the selected treatment option **426**, but may be temporarily discontinued from the existing course of treatment **428** by a period of three months or 90 days. The patient may be temporarily discontinued from the existing course of treatment **428** at any rate. Preferably, the patient may be temporarily discontinued from the existing course of treatment **428** when the major non-cranial hemorrhage are gastrointestinal, which may, for example, be at a probability of 89.9%. If the patient is predicted to suffer from a major non-cranial hemorrhage **420** and the simulation predicts that the patient is temporarily discontinued from the existing course of treatment **428**, a subsequent health state corresponding to the bleed event and the new course of treatment would be Health State 17 (step **1700**). If the patient is predicted to suffer from a major non-cranial hemorrhage **420** and the simulation predicts that the patient continues the existing course of treatment **430**, a subsequent health state would remain as Health State 4 (step **400**) to reflect the non-GI nature of the bleed event.

[0134] If the patient is predicted to suffer from a minor hemorrhage **422**, a subsequent health state would remain as Health State 4 (step **400**). Similarly, if the patient is predicted

not to experience an adverse event **408**, the simulation may predict that a subsequent health state would also remain as Health State 4 (step **400**).

Health State 5 (step **500**)

[0135] In Health State 5 (step **500**), the patient is predicted to have reversible ischemic stroke and under a course of treatment comprises administration of a particular treatment option to the patient. In this particular health state, the patient is not predicted to suffer from an adverse bleed event. For each iteration of the simulation, there is a predicted probability that the patient may die from adverse events unrelated to stroke and/or bleed events **502**, which includes adjustments to reflect an increased likelihood of death by other causes following a stroke, as well as the relative risk of death not caused by stroke or bleed events for a patient in NVAf under a particular treatment option (e.g., 1.3 for aspirin and 1.3 for warfarin). An exemplary increase of the relative risk of death by adverse events unrelated to stroke and/or bleed event after a patient suffers from a stroke may be 2.3. If the patient suffers from an adverse events unrelated to stroke and/or bleed events, a subsequent health state corresponding to this event would be Health State 31, death **3100**.

[0136] The patient may also experience stroke events **504**, bleed events **506**, or no adverse events **508**. The probability of the patient experiencing stroke events **504** may be determined using the baseline risk profile generated by a stroke index, such as, for example, the CHADS₂ scores and probabilities, which may be adjusted by the increase in relative risk of recurrent strokes and the relative risk for the selected treatment option as compared to aspirin. The relative risk of recurrent stroke may, for example, be at a rate of 2. If the patient is predicted to suffer from a stroke event **504**, the patient may experience a fatal event **510**, a moderate to severe ischemic stroke **512**, a mild ischemic stroke **514**, or a reversible ischemic stroke **516**. The probabilities of each of these stroke events may depend on the distribution of the severity of stroke events for the selected treatment option. For example, for a patient receiving warfarin, 8.2% of the stroke events are predicted to result in a fatal event **510**, 40.2% of the stroke events are predicted to result in moderate to severe ischemic stroke **512**, 42.5% of the stroke events are predicted to result in mild ischemic stroke **514**, and 9.1% of the stroke events are predicted to result in reversible ischemic stroke **516**. If the patient is predicted to suffer from a fatal event **510**, a subsequent health state corresponding to this event would be Health State 31, death **3100**. If the patient is predicted to suffer from moderate to severe ischemic stroke **512**, a subsequent health state corresponding to this event

would be Health State 6 (step **600**). If the patient is predicted to suffer from mild ischemic stroke **514**, a subsequent health state corresponding to this event would be Health State 6 (step **600**). If the patient is predicted to suffer from reversible ischemic stroke **516**, a subsequent health state corresponding to this event would be Health State 5 (step **500**).

[0137] The probability of the patient experiencing bleed events **506** may be determined using the baseline risk profile generated by a bleed index, such as, for example, the ATRIA scores and probabilities, which may be adjusted by the relative risk for the selected treatment option as compared to warfarin. If the patient is predicted to suffer from a bleed event **506**, the patient may experience a fatal event **518**, intra-cranial hemorrhage **520**, major non-cranial hemorrhage **522**, or minor hemorrhage **524**. The probabilities of each of these bleed events may depend on the distribution of the severity of bleed events for the selected treatment option. If the patient is predicted to suffer from a fatal event **518**, a subsequent health state corresponding to this event would be Health State 31, death **3100**. If the patient is predicted to suffer from intra-cranial hemorrhage **520**, a subsequent health state corresponding to this event would be Health State 13 (step **1300**).

[0138] If the patient is predicted to suffer from a major non-cranial hemorrhage **522**, the simulation may predict that the patient could be permanently discontinued from the treatment option **526** (e.g., administration of warfarin or aspirin), and a subsequent health state corresponding to the bleed event would be Health State 25 (step **2500**). The patient may be permanently discontinued from the treatment option **526** at any rate. Preferably, the patient may be permanently discontinued from the treatment option **526** at a probability of 25%. Alternatively, the patient may remain under the selected treatment option **528**, but may be temporarily discontinued **530** by a period of three months or 90 days. The patient may be temporarily discontinued **530** at any rate. Preferably, the patient may be temporarily discontinued from the existing course of treatment **530** when the major non-cranial hemorrhage are gastrointestinal, which may, for example, be at a probability of 89.9%. If the patient is predicted to suffer from a major non-cranial hemorrhage **522** and the simulation predicts that the patient is temporarily discontinued from the existing course of treatment **530**, a subsequent health state corresponding to the bleed event and the new course of treatment would be Health State 24 (step **2400**). If the patient is predicted to suffer from a major non-cranial hemorrhage **522** and the simulation predicts that the patient continues the existing course of treatment **532**, a subsequent health state corresponding to the bleed event and the

new course of treatment would be also be Health State 24 (step **2400**), because the existing course of treatment does not administer any particular treatment option to the patient.

[0139] If the patient is predicted to suffer from a minor hemorrhage **524**, a subsequent health state corresponding to the bleed event and the new course of treatment would be Health State 26 (step **2600**). If the patient is predicted not to experience an adverse event **508**, a subsequent health state corresponding to the bleed event and the new course of treatment would be Health State 1 (step **100**).

Health State 6 (step **600**)

[0140] In Health State 6 (step **600**), the patient is predicted to have recurrent stroke and under a course of treatment that comprises administration of a particular treatment option to the patient. In this particular health state, the patient is not predicted to suffer from an adverse bleed event. For each iteration of the simulation, there is a predicted probability that the patient may die from adverse events unrelated to stroke and/or bleed events **602**, which includes adjustments to reflect an increased likelihood of death by other causes following a stroke, as well as the relative risk of death not caused by stroke or bleed events for a patient in NVAf under a particular treatment option (e.g., 1.3 for aspirin and 1.3 for warfarin). An exemplary increase of the relative risk of death by adverse events unrelated to stroke and/or bleed event after a patient suffers from a stroke may be 2.3. If the patient suffers from an adverse events unrelated to stroke and/or bleed events, a subsequent health state corresponding to this event would be Health State 31, death **3100**.

[0141] The patient may also experience stroke events **604**, bleed events **606**, or no adverse events **608**. The probability of the patient experiencing stroke events **604** may be determined using the baseline risk profile generated by a stroke index, such as, for example, the CHADS₂ scores and probabilities, which may be adjusted by the increase in relative risk of recurrent strokes and the relative risk for the selected treatment option as compared to aspirin. The relative risk of recurrent stroke may, for example, be at a rate of 2. If the patient is predicted to suffer from a stroke event **604**, the patient may experience a fatal event **610**, a moderate to severe ischemic stroke **612**, or a mild ischemic stroke **614**. The probabilities of each of these stroke events may depend on the distribution of the severity of stroke events for the selected treatment option. If the patient is predicted to suffer from a fatal event **610**, a subsequent health state corresponding to this event would be Health State 31, death **3100**. If

the patient is predicted to suffer from moderate to severe ischemic stroke **612** or mild ischemic stroke **614**, the simulation also predicts that the patient will die (Health State 31, step **3100**) from such a stroke event because of the patient's severely diminished health in this health state, the patient is not likely to survive an additional stroke.

[0142] The probability of the patient experiencing bleed events **606** may be determined using the baseline risk profile generated by a bleed index, such as, for example, the ATRIA scores and probabilities, which may be adjusted by the relative risk for the selected treatment option as compared to warfarin. If the patient is predicted to suffer from a bleed event **606**, the patient may experience a fatal event **616**, intra-cranial hemorrhage **618**, major non-cranial hemorrhage **620**, or minor hemorrhage **622**. The probabilities of each of these bleed events may depend on the distribution of the severity of bleed events for the selected treatment option. If the patient is predicted to suffer from a fatal event **616**, a subsequent health state corresponding to this event would be Health State 31, death **3100**. If the patient is predicted to suffer from intra-cranial hemorrhage **618**, the simulation also predicts that the patient will die (Health State 31, step **3100**) from such a bleed event because of the patient's severely diminished health in this health state, the patient is not likely to survive an intra-cranial hemorrhage.

[0143] If the patient is predicted to suffer from a major non-cranial hemorrhage **620**, the simulation may predict that the patient could be permanently discontinued from the existing course of treatment **624**, which is the administration of the selected treatment option, and a subsequent health state corresponding to the bleed event and the new course of treatment would be Health State 22 (step **2200**). The patient may be permanently discontinued from the existing course of treatment **624** at any rate. Preferably, the patient may be permanently discontinued from the existing course of treatment **624** at a probability of 25%. Alternatively, the patient may remain under the selected treatment option **626**, but may be temporarily discontinued from the existing course of treatment **628** by a period of three months or 90 days. The patient may be temporarily discontinued from the existing course of treatment **628** at any rate. Preferably, the patient may be temporarily discontinued from the existing course of treatment **628** when the major non-cranial hemorrhage are gastrointestinal, which may, for example, be at a probability of 89.9%. If the patient is predicted to suffer from a major non-cranial hemorrhage **620** and the simulation predicts that the patient is temporarily discontinued from the existing course of treatment **628**, a

subsequent health state corresponding to the bleed event and the new course of treatment would be Health State 20 (step **2000**). If the patient is predicted to suffer from a major non-cranial hemorrhage **620** and the simulation predicts that the patient continues the existing course of treatment **630**, a subsequent health state would remain as Health State 6 (step **600**) to reflect the non-GI nature of the bleed event.

[0144] If the patient is predicted to suffer from a minor hemorrhage **622**, a subsequent health state would remain as Health State 6 (step **600**). Similarly, if the patient is predicted not to experience an adverse event **608**, the simulation may predict that a subsequent health state would also remain as Health State 4 (step **600**).

Health State 7 (step **700**)

[0145] In Health State 7 (step **700**), the patient is predicted to have intra-cranial hemorrhage and is permanently discontinued from the treatment option. In this particular health state, the patient is not predicted to suffer from an adverse stroke event. For each iteration of the simulation, there is a predicted probability that the patient may die from adverse events unrelated to stroke and/or bleed events **702**, which includes adjustments to reflect an increased likelihood of death by other causes following an intracranial hemorrhage, as well as the relative risk of death not caused by stroke or bleed events for a patient in NVAf under a particular treatment option (e.g., 1.3 for aspirin and 1.3 for warfarin). An exemplary increase of the relative risk of death by adverse events unrelated to stroke and/or bleed event after a patient suffers from a intracranial hemorrhage may be 2.3. If the patient suffers from an adverse events unrelated to stroke and/or bleed events, a subsequent health state corresponding to this event would be Health State 31, death **3100**.

[0146] The patient may also experience stroke events **704**, bleed events **706**, or no adverse events **708**. The probability of the patient experiencing stroke events **704** may be determined using the baseline risk profile generated by a stroke index, such as, for example, the CHADS₂ scores and probabilities, which may be adjusted by the relative risk for the selected treatment option as compared to aspirin. If the patient is predicted to suffer from a stroke event **704**, the patient may experience a fatal event **710**, a moderate to severe ischemic stroke **712**, a mild ischemic stroke **714**, or a reversible ischemic stroke **716**. The probabilities of each of these stroke events may depend on the distribution of the severity of stroke events for the selected treatment option. If the patient is predicted to suffer from a fatal event **710**, a

subsequent health state corresponding to this event would be Health State 31, death **3100**. If the patient is predicted to suffer from moderate to severe ischemic stroke **712**, a subsequent health state corresponding to this event would be Health State 12 (step **1200**). If the patient is predicted to suffer from mild ischemic stroke **714**, a subsequent health state corresponding to this event would also be Health State 12 (step **1200**). If the patient is predicted to suffer from reversible ischemic stroke **716**, a subsequent health state corresponding to this event would be Health State 13 (step **1300**).

[0147] The probability of the patient experiencing bleed events **706** may be determined using the baseline risk profile generated by a bleed index, such as, for example, the ATRIA scores and probabilities, which may be adjusted by the increase in relative risk of recurrent bleeds and the relative risk for the selected treatment option as compared to warfarin. The relative risk of recurrent bleed may, for example, be at a rate of 1.5. If the patient is predicted to suffer from a bleed event **706**, the patient may experience a fatal event **718**, intra-cranial hemorrhage **720**, major non-cranial hemorrhage **722**, or minor hemorrhage **724**. The probabilities of each of these bleed events may depend on the distribution of the severity of bleed events for the selected treatment option. If the patient is predicted to suffer from a fatal event **718**, a subsequent health state corresponding to this event would be Health State 31, death **3100**. If the patient is predicted to suffer from intra-cranial hemorrhage **720**, a subsequent health state corresponding to this event would be Health State 7 (step **700**). If the patient is predicted to suffer from a major non-cranial hemorrhage **722**, a subsequent health state corresponding to this event would be Health State 11 (step **1100**).

[0148] If the patient is predicted to suffer from a minor hemorrhage **624**, a subsequent health state would remain as Health State 7 (step **700**). Similarly, if the patient is predicted not to experience an adverse event **708**, the simulation may predict that a subsequent health state would also remain as Health State 7 (step **700**).

Health State 8 (step **800**)

[0149] In Health State 8 (step **800**), the patient is predicted to have a major non-cranial hemorrhage and is temporarily discontinued from the treatment option. In this particular health state, the patient is not predicted to suffer from an adverse stroke event. For each iteration of the simulation, there is a predicted probability that the patient may die from adverse events unrelated to stroke and/or bleed events **802**, which includes adjustments to

reflect an increased likelihood of death by other causes following an intracranial hemorrhage, as well as the relative risk of death not caused by stroke or bleed events for a patient in NVAf under a particular treatment option (e.g., 1.3 for aspirin and 1.3 for warfarin). An exemplary increase of the relative risk of death by adverse events unrelated to stroke and/or bleed event after a patient suffers from an intracranial hemorrhage may be 2.3. If the patient suffers from an adverse events unrelated to stroke and/or bleed events, a subsequent health state corresponding to this event would be Health State 31, death **3100**.

[0150] The patient may also experience stroke events **804**, bleed events **806**, or no adverse events **808**. The probability of the patient experiencing stroke events **804** may be determined using the baseline risk profile generated by a stroke index, such as, for example, the CHADS₂ scores and probabilities, which may be adjusted by the relative risk for the selected treatment option as compared to aspirin. If the patient is predicted to suffer from a stroke event **804**, the patient may experience a fatal event **810**, a moderate to severe ischemic stroke **812**, a mild ischemic stroke **814**, or a reversible ischemic stroke **816**. The probabilities of each of these stroke events may depend on the distribution of the severity of stroke events for the selected treatment option. If the patient is predicted to suffer from a fatal event **810**, a subsequent health state corresponding to this event would be Health State 31, death **3100**. If the patient is predicted to suffer from moderate to severe ischemic stroke **812**, a subsequent health state corresponding to this event would be Health State 15 (step **1500**). If the patient is predicted to suffer from mild ischemic stroke **814**, a subsequent health state corresponding to this event would also be Health State 18 (step **1800**). If the patient is predicted to suffer from reversible ischemic stroke **816**, a subsequent health state corresponding to this event would be Health State 24 (step **2400**).

[0151] The probability of the patient experiencing bleed events **806** may be determined using the baseline risk profile generated by a bleed index, such as, for example, the ATRIA scores and probabilities, which may be adjusted by the increase in relative risk of recurrent bleeds and the relative risk for the selected treatment option as compared to warfarin. The relative risk of recurrent bleed may, for example, be at a rate of 1.5. If the patient is predicted to suffer from a bleed event **806**, the patient may experience a fatal event **818**, intra-cranial hemorrhage **820**, major non-cranial hemorrhage **822**, or minor hemorrhage **824**. The probabilities of each of these bleed events may depend on the distribution of the severity of bleed events for the selected treatment option. If the patient is predicted to suffer

from a fatal event **818**, a subsequent health state corresponding to this event would be Health State 31, death **3100**. If the patient is predicted to suffer from intra-cranial hemorrhage **820**, a subsequent health state corresponding to this event would be Health State 10 (step **1000**).

[0152] If the patient is predicted to suffer from a major non-cranial hemorrhage **822**, the simulation may predict that the patient could be permanently discontinued from the existing course of treatment **826**, which is the administration of the selected treatment option, and a subsequent health state corresponding to the bleed event and the new course of treatment would be Health State 10 (step **1000**). The patient may be permanently discontinued from the existing course of treatment **826** at any rate. Preferably, the patient may be permanently discontinued from the existing course of treatment **826** at a probability of 25%. Alternatively, the patient may remain under the selected treatment option **828**, but may be temporarily discontinued from the existing course of treatment **830** by a period of three months or 90 days. The patient may be temporarily discontinued from the existing course of treatment **830** at any rate. Preferably, the patient may be temporarily discontinued from the existing course of treatment **830** when the major non-cranial hemorrhage are gastrointestinal, which may, for example, be at a probability of 89.9%. If the patient is predicted to suffer from a major non-cranial hemorrhage **822** and the simulation predicts that the patient is temporarily discontinued from the existing course of treatment **830**, a subsequent health state corresponding to the bleed event and the new course of treatment would be Health State 8 (step **800**). If the patient is predicted to suffer from a major non-cranial hemorrhage **822** and the simulation predicts that the patient continues the existing course of treatment **832**, a subsequent health state corresponding to the bleed event and the new course of treatment would be Health State 9 (step **900**).

[0153] If the patient is predicted to suffer from a minor hemorrhage **824**, the simulation may predict that the patient could be discontinued from the existing course of treatment **834**, and a subsequent health state corresponding to the bleed event and the new course of treatment would be Health State 28 (step **2800**). If the patient is predicted to suffer from a minor hemorrhage **824**, the simulation may predict that the patient would continue the existing course of treatment **836**, and a subsequent health state would remain as Health State 27 (step **2700**). The patient may be discontinued from the existing course of treatment **834** and/or continue the selected treatment option **836** at any rate. Moreover, the probability of continuing a treatment option following a minor bleed **836** may be lower for warfarin than for

other treatment options. For example, the probability of continuing warfarin following a minor bleed may be 60% per year, where as the probability of continuing other treatment options (e.g., aspirin, or edoxaban) may be 95% per year.

[0154] If the patient is predicted not to experience an adverse event **808**, the simulation may predict that the patient may be adherent and continue the existing course of treatment **840** or non-adherent and discontinue the existing course of treatment **838**. If the patient is adherent **840**, then the subsequent health state would remain as Health State 27 (step **2700**). If the patient is non-adherent **838**, then the subsequent health state would be Health State 28 (step **2800**) to reflect the condition of the patient and the new course of treatment. The patient's adherence and non-adherence to the existing course of treatment may be at any rate. Moreover, the probability of continuing a treatment option **840** may be lower for warfarin than for other treatment options. For example, the probability of continuing warfarin may be 60% per year, where as the probability of continuing other treatment options (e.g., aspirin, or edoxaban) may be 95% per year. The probabilities applied to the simulation may be adjusted based on the period of life predicted by an iteration of the simulation.

Health State 9 (step **900**)

[0155] In Health State 9 (step **900**), the patient is predicted to have a major non-cranial hemorrhage and under a course of treatment that comprises administration of a particular treatment option to the patient. In this particular health state, the patient is not predicted to suffer from an adverse stroke event. For each iteration of the simulation, there is a predicted probability that the patient may die from adverse events unrelated to stroke and/or bleed events **902**, which includes adjustments to reflect an increased likelihood of death by other causes following an intracranial hemorrhage, as well as the relative risk of death not caused by stroke or bleed events for a patient in NVAf under a particular treatment option (e.g., 1.3 for aspirin and 1.3 for warfarin). An exemplary increase of the relative risk of death by adverse events unrelated to stroke and/or bleed event after a patient suffers from a intracranial hemorrhage may be 2.3. If the patient suffers from an adverse events unrelated to stroke and/or bleed events, a subsequent health state corresponding to this event would be Health State 31, death **3100**.

[0156] The patient may also experience stroke events **904**, bleed events **906**, or no adverse events **908**. The probability of the patient experiencing stroke events **904** may be determined using the baseline risk profile generated by a stroke index, such as, for example, the CHADS₂ scores and probabilities, which may be adjusted by the relative risk for the selected treatment option as compared to aspirin. If the patient is predicted to suffer from a stroke event **904**, the patient may experience a fatal event **910**, a moderate to severe ischemic stroke **912**, a mild ischemic stroke **914**, or a reversible ischemic stroke **916**. The probabilities of each of these stroke events may depend on the distribution of the severity of stroke events for the selected treatment option. If the patient is predicted to suffer from a fatal event **910**, a subsequent health state corresponding to this event would be Health State 31, death **3100**. If the patient is predicted to suffer from moderate to severe ischemic stroke **912**, a subsequent health state corresponding to this event would be Health State 15 (step **1500**). If the patient is predicted to suffer from mild ischemic stroke **914**, a subsequent health state corresponding to this event would also be Health State 18 (step **1800**). If the patient is predicted to suffer from reversible ischemic stroke **916**, a subsequent health state corresponding to this event would be Health State 23 (step **2300**).

[0157] The probability of the patient experiencing bleed events **906** may be determined using the baseline risk profile generated by a bleed index, such as, for example, the ATRIA scores and probabilities, which may be adjusted by the increase in relative risk of recurrent bleeds and the relative risk for the selected treatment option as compared to warfarin. The relative risk of recurrent bleed may, for example, be at a rate of 1.5. If the patient is predicted to suffer from a bleed event **906**, the patient may experience a fatal event **918**, intra-cranial hemorrhage **920**, major non-cranial hemorrhage **922**, or minor hemorrhage **924**. The probabilities of each of these bleed events may depend on the distribution of the severity of bleed events for the selected treatment option. If the patient is predicted to suffer from a fatal event **918**, a subsequent health state corresponding to this event would be Health State 31, death **3100**. If the patient is predicted to suffer from intra-cranial hemorrhage **920**, a subsequent health state corresponding to this event would be Health State 11 (step **1100**).

[0158] If the patient is predicted to suffer from a major non-cranial hemorrhage **922**, the simulation may predict that the patient could be permanently discontinued from the existing course of treatment **926**, which is the administration of the selected treatment option, and a subsequent health state corresponding to the bleed event and the new course of

treatment would be Health State 10 (step **1000**). The patient may be permanently discontinued from the existing course of treatment **926** at any rate. Preferably, the patient may be permanently discontinued from the existing course of treatment **926** at a probability of 25%. Alternatively, the patient may remain under the selected treatment option **928**, but may be temporarily discontinued from the existing course of treatment **930** by a period of three months or 90 days. The patient may be temporarily discontinued from the existing course of treatment **930** at any rate. Preferably, the patient may be temporarily discontinued from the existing course of treatment **930** when the major non-cranial hemorrhage are gastrointestinal, which may, for example, be at a probability of 89.9%. If the patient is predicted to suffer from a major non-cranial hemorrhage **922** and the simulation predicts that the patient is temporarily discontinued from the existing course of treatment **930**, a subsequent health state corresponding to the bleed event and the new course of treatment would be Health State 8 (step **800**). If the patient is predicted to suffer from a major non-cranial hemorrhage **922** and the simulation predicts that the patient continues the existing course of treatment **932**, a subsequent health state corresponding to the bleed event would be Health State 9 (step **900**).

[0159] If the patient is predicted to suffer from a minor hemorrhage **924**, the simulation may predict that the patient could be discontinued from the existing course of treatment **934**, and a subsequent health state corresponding to the bleed event and the new course of treatment would be Health State 28 (step **2800**). If the patient is predicted to suffer from a minor hemorrhage **924**, the simulation may predict that the patient would continue the existing course of treatment **936**, and a subsequent health state would remain as Health State 27 (step **2700**). The patient may be discontinued from the existing course of treatment **934** and/or continue the selected treatment option **936** at any rate. Moreover, the probability of continuing a treatment option following a minor bleed **936** may be lower for warfarin than for other treatment options. For example, the probability of continuing warfarin following a minor bleed may be 60% per year, where as the probability of continuing other treatment options (e.g., aspirin, or edoxaban) may be 95% per year.

[0160] If the patient is predicted not to experience an adverse event **908**, the simulation may predict that the patient may be adherent and continue the existing course of treatment **940** or non-adherent and discontinue the existing course of treatment **938**. If the patient is adherent **940**, then the subsequent health state would remain as Health State 27

(step **2700**). If the patient is non-adherent **938**, then the subsequent health state would be Health State 28 (step **2800**) to reflect the condition of the patient and the new course of treatment. The patient's adherence and non-adherence to the existing course of treatment may be at any rate. Moreover, the probability of continuing a treatment option **940** may be lower for warfarin than for other treatment options. For example, the probability of continuing warfarin may be 60% per year, where as the probability of continuing other treatment options (e.g., aspirin, or edoxaban) may be 95% per year. The probabilities applied to the simulation may be adjusted based on the period of life predicted by an iteration of the simulation.

Health State 10 (step **1000**)

[0161] In Health State 10 (step **1000**), the patient is predicted to have a major non-cranial hemorrhage and is permanently discontinued from the treatment option. In this particular health state, the patient is not predicted to suffer from an adverse stroke event. For each iteration of the simulation, there is a predicted probability that the patient may die from adverse events unrelated to stroke and/or bleed events **1002**, which includes adjustments to reflect an increased likelihood of death by other causes following an intracranial hemorrhage, as well as the relative risk of death not caused by stroke or bleed events for a patient in NVAf under a particular treatment option (e.g., 1.3 for aspirin and 1.3 for warfarin). An exemplary increase of the relative risk of death by adverse events unrelated to stroke and/or bleed event after a patient suffers from a intracranial hemorrhage may be 2.3. If the patient suffers from an adverse events unrelated to stroke and/or bleed events, a subsequent health state corresponding to this event would be Health State 31, death **3100**.

[0162] The patient may also experience stroke events **1004**, bleed events **1006**, or no adverse events **1008**. The probability of the patient experiencing stroke events **1004** may be determined using the baseline risk profile generated by a stroke index, such as, for example, the CHADS₂ scores and probabilities, which may be adjusted by the relative risk for the selected treatment option as compared to aspirin. If the patient is predicted to suffer from a stroke event **1004**, the patient may experience a fatal event **1010**, a moderate to severe ischemic stroke **1012**, a mild ischemic stroke **1014**, or a reversible ischemic stroke **1016**. The probabilities of each of these stroke events may depend on the distribution of the severity of stroke events for the selected treatment option. If the patient is predicted to suffer from a fatal event **1010**, a subsequent health state corresponding to this event would be Health State

31, death **3100**. If the patient is predicted to suffer from moderate to severe ischemic stroke **1012**, a subsequent health state corresponding to this event would be Health State 16 (step **1600**). If the patient is predicted to suffer from mild ischemic stroke **1014**, a subsequent health state corresponding to this event would also be Health State 19 (step **1900**). If the patient is predicted to suffer from reversible ischemic stroke **1016**, a subsequent health state corresponding to this event would be Health State 25 (step **2500**).

[**0163**] The probability of the patient experiencing bleed events **1006** may be determined using the baseline risk profile generated by a bleed index, such as, for example, the ATRIA scores and probabilities, which may be adjusted by the increase in relative risk of recurrent bleeds and the relative risk for the selected treatment option as compared to warfarin. The relative risk of recurrent bleed may, for example, be at a rate of 1.5. If the patient is predicted to suffer from a bleed event **1006**, the patient may experience a fatal event **1018**, intra-cranial hemorrhage **1020**, major non-cranial hemorrhage **1022**, or minor hemorrhage **1024**. The probabilities of each of these bleed events may depend on the distribution of the severity of bleed events for the selected treatment option. If the patient is predicted to suffer from a fatal event **1018**, a subsequent health state corresponding to this event would be Health State 31, death **3100**. If the patient is predicted to suffer from intra-cranial hemorrhage **1020**, a subsequent health state corresponding to this event would be Health State 11 (step **1100**).

[**0164**] If the patient is predicted to suffer from a major non-cranial hemorrhage **1022**, the simulation may predict that the patient could be permanently discontinued from the existing course of treatment **1026**, which is the administration of the selected treatment option, and a subsequent health state corresponding to the bleed event and the new course of treatment would be Health State 10 (step **1000**). The patient may be permanently discontinued from the existing course of treatment **1026** at any rate. Preferably, the patient may be permanently discontinued from the existing course of treatment **1026** at a probability of 25%. Alternatively, the patient may remain under the selected treatment option **1028**, but may be temporarily discontinued from the existing course of treatment **1030** by a period of three months or 90 days. The patient may be temporarily discontinued from the existing course of treatment **1030** at any rate. Preferably, the patient may be temporarily discontinued from the existing course of treatment **1030** when the major non-cranial hemorrhage are gastrointestinal, which may, for example, be at a probability of 89.9%. If the patient is

predicted to suffer from a major non-cranial hemorrhage **1022** and the simulation predicts that the patient is temporarily discontinued from the existing course of treatment **1030**, a subsequent health state corresponding to the bleed event and the new course of treatment would be Health State 10 (step **1000**). If the patient is predicted to suffer from a major non-cranial hemorrhage **1022** and the simulation predicts that the patient continues the existing course of treatment **1032**, a subsequent health state corresponding to the bleed event would be Health State 10 (step **1000**).

[0165] If the patient is predicted to suffer from a minor hemorrhage **1024**, a subsequent health state would remain as Health State 28 (step **2800**). Similarly, if the patient is predicted not to experience an adverse event **1008**, the simulation may predict that a subsequent health state would also remain as Health State 28 (step **2800**).

Health State 11 (step **1100**)

[0166] In Health State 11 (step **1100**), the patient is predicted to have recurrent bleed and is permanently discontinued from the treatment option. In this particular health state, the patient is not predicted to suffer from an adverse stroke event. For each iteration of the simulation, there is a predicted probability that the patient may die from adverse events unrelated to stroke and/or bleed events **1102**, which includes adjustments to reflect an increased likelihood of death by other causes following an intracranial hemorrhage, as well as the relative risk of death not caused by stroke or bleed events for a patient in NVAf under a particular treatment option (e.g., 1.3 for aspirin and 1.3 for warfarin). An exemplary increase of the relative risk of death by adverse events unrelated to stroke and/or bleed event after a patient suffers from an intracranial hemorrhage may be 2.3. If the patient suffers from an adverse events unrelated to stroke and/or bleed events, a subsequent health state corresponding to this event would be Health State 31, death **3100**.

[0167] The patient may also experience stroke events **1104**, bleed events **1106**, or no adverse events **1108**. The probability of the patient experiencing stroke events **1104** may be determined using the baseline risk profile generated by a stroke index, such as, for example, the CHADS₂ scores and probabilities, which may be adjusted by the relative risk for the selected treatment option as compared to aspirin. If the patient is predicted to suffer from a stroke event **1104**, the patient may experience a fatal event **1110**, a moderate to severe ischemic stroke **1112**, a mild ischemic stroke **1114**, or a reversible ischemic stroke **1116**. The

probabilities of each of these stroke events may depend on the distribution of the severity of stroke events for the selected treatment option. If the patient is predicted to suffer from a fatal event **1110**, a subsequent health state corresponding to this event would be Health State 31, death **3100**. If the patient is predicted to suffer from moderate to severe ischemic stroke **1112** or mild ischemic stroke **1114**, the simulation also predicts that the patient will die (Health State 31, step **3100**) from such a stroke event, because of the patient suffers from severely diminished health in this health state and would not likely to survive a major stroke event. If the patient is predicted to suffer from reversible ischemic stroke **1116**, a subsequent health state corresponding to this event would be Health State 11(step **1100**).

[0168] The probability of the patient experiencing bleed events **1106** may be determined using the baseline risk profile generated by a bleed index, such as, for example, the ATRIA scores and probabilities, which may be adjusted by the increase in relative risk of recurrent bleeds and the relative risk for the selected treatment option as compared to warfarin. The relative risk of recurrent bleed may, for example, be at a rate of 1.5. If the patient is predicted to suffer from a bleed event **1106**, the patient may experience a fatal event **1118**, intra-cranial hemorrhage **1120**, major non-cranial hemorrhage **1122**, or minor hemorrhage **1124**. The probabilities of each of these bleed events may depend on the distribution of the severity of bleed events for the selected treatment option. If the patient is predicted to suffer from a fatal event **1118**, a subsequent health state corresponding to this event would be Health State 31, death **3100**. If the patient is predicted to suffer from intra-cranial hemorrhage **1118**, the simulation also predicts that the patient will die (Health State 31, step **3100**) because of the patient suffers from severely diminished health in this health state and would not likely to survive an intra-cranial hemorrhage.

[0169] If the patient is predicted to suffer from a major non-cranial hemorrhage **1122**, the simulation may predict that the patient could be permanently discontinued from the existing course of treatment **1126**, which is the administration of the selected treatment option, and a subsequent health state will remain as Health State 11 (step **1100**). The patient may be permanently discontinued from the existing course of treatment **1126** at any rate. Preferably, the patient may be permanently discontinued from the existing course of treatment **1126** at a probability of 25%. Alternatively, the patient may remain under the selected treatment option **1128**, but may be temporarily discontinued from the existing course of treatment **1130** by a period of three months or 90 days. The patient may be temporarily

discontinued from the existing course of treatment **1130** at any rate. Preferably, the patient may be temporarily discontinued from the existing course of treatment **1130** when the major non-cranial hemorrhage are gastrointestinal, which may, for example, be at a probability of 89.9%. If the patient is predicted to suffer from a major non-cranial hemorrhage **1122** and the simulation predicts that the patient is temporarily discontinued from the existing course of treatment **1130**, a subsequent health state may remain as Health State 11 (step **1100**). If the patient is predicted to suffer from a major non-cranial hemorrhage **1122** and the simulation predicts that the patient continues the existing course of treatment **1132**, a subsequent health state may remain as Health State 11 (step **1100**). If the patient is predicted to suffer from a minor hemorrhage **1124**, a subsequent health state would remain as Health State 11 (step **1100**). Similarly, if the patient is predicted not to experience an adverse event **1108**, the simulation may predict that a subsequent health state would also remain as Health State 11 (step **1100**).

Health State 12 (step **1200**)

[0170] In Health State 12 (step **1200**), the patient is predicted to have a stroke causing permanent disability and an intra-cranial hemorrhage and is permanently discontinued from the treatment option. For each iteration of the simulation, there is a predicted probability that the patient may die from adverse events unrelated to stroke and/or bleed events **1202**, which includes adjustments to reflect an increased likelihood of death by other causes following an intracranial hemorrhage and stroke, as well as the relative risk of death not caused by stroke or bleed events for a patient in NVAf under a particular treatment option (e.g., 1.3 for aspirin and 1.3 for warfarin). An exemplary increase of the relative risk of death by adverse events unrelated to stroke and/or bleed event after a patient suffers from an intracranial hemorrhage and stroke may be 2.3. If the patient suffers from an adverse events unrelated to stroke and/or bleed events, a subsequent health state corresponding to this event would be Health State 31, death **3100**.

[0171] The patient may also experience stroke events **1204**, bleed events **1206**, or no adverse events **1208**. The probability of the patient experiencing stroke events **1204** may be determined using the baseline risk profile generated by a stroke index, such as, for example, the CHADS₂ scores and probabilities, which may be adjusted by the increase in relative risk of recurrent strokes and the relative risk for the selected treatment option as compared to aspirin. The relative risk of recurrent stroke may, for example, be at a rate of 2. If the patient

is predicted to suffer from a stroke event **1204**, the patient may experience a fatal event **1210**, a moderate to severe ischemic stroke **1212**, or a mild ischemic stroke **1214**. The probabilities of each of these stroke events may depend on the distribution of the severity of stroke events for the selected treatment option. If the patient is predicted to suffer from a fatal event **1210**, a subsequent health state corresponding to this event would be Health State 31, death **3100**. If the patient is predicted to suffer from moderate to severe ischemic stroke **1212** or mild ischemic stroke **1214**, the simulation also predicts that the patient will die (Health State 31, step **3100**) from such a stroke event, because of the patient suffers from severely diminished health in this health state and would not likely to survive a major stroke event.

[0172] The probability of the patient experiencing bleed events **1206** may be determined using the baseline risk profile generated by a bleed index, such as, for example, the ATRIA scores and probabilities, which may be adjusted by the increase in relative risk of recurrent bleeds and the relative risk for the selected treatment option as compared to warfarin. The relative risk of recurrent bleed may, for example, be at a rate of 1.5. If the patient is predicted to suffer from a bleed event **1206**, the patient may experience a fatal event **1216**, intra-cranial hemorrhage **1218**, major non-cranial hemorrhage **1220**, or minor hemorrhage **1222**. The probabilities of each of these bleed events may depend on the distribution of the severity of bleed events for the selected treatment option. If the patient is predicted to suffer from a fatal event **1216**, a subsequent health state corresponding to this event would be Health State 31, death **3100**. If the patient is predicted to suffer from intra-cranial hemorrhage **1218**, the simulation also predicts that the patient will die (Health State 31, step **3100**) because of the patient suffers from severely diminished health in this health state and would not likely to survive an intra-cranial hemorrhage.

[0173] If the patient is predicted to suffer from a major non-cranial hemorrhage **1220**, a subsequent health state would remain as Health State 12 (step **1200**). If the patient is predicted to suffer from a minor hemorrhage **1222**, a subsequent health state would also remain as Health State 12 (step **1200**). Similarly, if the patient is predicted not to experience an additional adverse event **1208**, the simulation may predict that a subsequent health state would remain as Health State 12 (step **1200**).

Health State 13 (step **1300**).

[0174] In Health State 13 (step **1300**), the patient is predicted to have a reversible ischemic stroke and an intra-cranial hemorrhage and is permanently discontinued from the treatment option. For each iteration of the simulation, there is a predicted probability that the patient may die from adverse events unrelated to stroke and/or bleed events **1302**, which includes adjustments to reflect an increased likelihood of death by other causes following an intracranial hemorrhage and stroke, as well as the relative risk of death not caused by stroke or bleed events for a patient in NVAF under a particular treatment option (e.g., 1.3 for aspirin and 1.3 for warfarin). An exemplary increase of the relative risk of death by adverse events unrelated to stroke and/or bleed event after a patient suffers from an intracranial hemorrhage and stroke may be 2.3. If the patient suffers from an adverse events unrelated to stroke and/or bleed events, a subsequent health state corresponding to this event would be Health State 31, death **3100**.

[0175] The patient may also experience stroke events **1304**, bleed events **1306**, or no adverse events **1308**. The probability of the patient experiencing stroke events **1304** may be determined using the baseline risk profile generated by a stroke index, such as, for example, the CHADS₂ scores and probabilities, which may be adjusted by the increase in relative risk of recurrent strokes and the relative risk for the selected treatment option as compared to aspirin. The relative risk of recurrent stroke may, for example, be at a rate of 2. If the patient is predicted to suffer from a stroke event **1304**, the patient may experience a fatal event **1310**, a moderate to severe ischemic stroke **1312**, a mild ischemic stroke **1314**, or a reversible ischemic stroke **1316**. The probabilities of each of these stroke events may depend on the distribution of the severity of stroke events for the selected treatment option. If the patient is predicted to suffer from a fatal event **1310**, a subsequent health state corresponding to this event would be Health State 31, death **3100**. If the patient is predicted to suffer from moderate to severe ischemic stroke **1312**, a subsequent health state corresponding to this event would be Health State 12 (step **1200**). If the patient is predicted to suffer from mild ischemic stroke **1314**, a subsequent health state corresponding to this event would also be Health State 12 (step **1300**). If the patient is predicted to suffer from reversible ischemic stroke **1316**, a subsequent health state corresponding to this event would be Health State 13 (step **1300**).

[0176] The probability of the patient experiencing bleed events **1306** may be determined using the baseline risk profile generated by a bleed index, such as, for example,

the ATRIA scores and probabilities, which may be adjusted by the increase in relative risk of recurrent bleeds and the relative risk for the selected treatment option as compared to warfarin. The relative risk of recurrent bleed may, for example, be at a rate of 1.5. If the patient is predicted to suffer from a bleed event **1306**, the patient may experience a fatal event **1318**, intra-cranial hemorrhage **1320**, major non-cranial hemorrhage **1322**, or minor hemorrhage **1324**. The probabilities of each of these bleed events may depend on the distribution of the severity of bleed events for the selected treatment option. If the patient is predicted to suffer from a fatal event **1318**, a subsequent health state corresponding to this event would be Health State 31, death **3100**. If the patient is predicted to suffer from intra-cranial hemorrhage **1320**, a subsequent health state corresponding to this event would be Health State 11 (step **1100**). If the patient is predicted to suffer from a major non-cranial hemorrhage **1322**, a subsequent health state corresponding to this event would also be Health State 11 (step **1100**).

[0177] If the patient is predicted to suffer from a minor hemorrhage **1324**, a subsequent health state would remain as Health State 13 (step **1300**). Similarly, if the patient is predicted not to experience an adverse event **1308**, the simulation may predict that a subsequent health state would also remain as Health State 13 (step **1300**).

Health State 14 (step **1400**)

[0178] In Health State 14 (step **1400**), the patient is predicted to have a moderate to severe ischemic stroke and major non-cranial hemorrhage and is temporarily discontinued from the treatment option. For each iteration of the simulation, there is a predicted probability that the patient may die from adverse events unrelated to stroke and/or bleed events **1402**, which includes adjustments to reflect an increased likelihood of death by other causes following a stroke, as well as the relative risk of death not caused by stroke or bleed events for a patient in NVAf under a particular treatment option (e.g., 1.3 for aspirin and 1.3 for warfarin). An exemplary increase of the relative risk of death by adverse events unrelated to stroke and/or bleed event after a patient suffers from a stroke may be 2.3. If the patient suffers from an adverse events unrelated to stroke and/or bleed events, a subsequent health state corresponding to this event would be Health State 31, death **3100**.

[0179] The patient may also experience stroke events **1404**, bleed events **1406**, or no adverse events **1408**. The probability of the patient experiencing stroke events **1404** may be

determined using the baseline risk profile generated by a stroke index, such as, for example, the CHADS₂ scores and probabilities, which may be adjusted by the increase in relative risk of recurrent strokes and the relative risk for the selected treatment option as compared to aspirin. The relative risk of recurrent stroke may, for example, be at a rate of 2. If the patient is predicted to suffer from a stroke event **1404**, the patient may experience a fatal event **1410** or a moderate to severe ischemic stroke **1412**. The probabilities of each of these stroke events may depend on the distribution of the severity of stroke events for the selected treatment option. For example, for a patient receiving warfarin, 8.2% of the stroke events are predicted to result in a fatal event **1410**, the remainder of the stroke events is predicted to result in moderate to severe ischemic stroke **1412**. If the patient is predicted to suffer from a fatal event **1410**, a subsequent health state corresponding to this event would be Health State 31, death **3100**. If the patient is predicted to suffer from moderate to severe ischemic stroke **1412**, a subsequent health state corresponding to this event would be Health State 6 (step **600**), which reflects the patient having suffered from a recurrent stroke, after having already experienced a moderate to severe ischemic stroke, which is one of the existing conditions represented by Health State 14 (step **1400**).

[0180] The probability of the patient experiencing bleed events **1406** may be determined using the baseline risk profile generated by a bleed index, such as, for example, the ATRIA scores and probabilities, which may be adjusted by the increase in relative risk of recurrent bleeds and the relative risk for the selected treatment option as compared to warfarin. The relative risk of recurrent bleed may, for example, be at a rate of 1.5. If the patient is predicted to suffer from a bleed event **1406**, the patient may experience a fatal event **1414**, intra-cranial hemorrhage **1416**, major non-cranial hemorrhage **1418**, or minor hemorrhage **1420**. The probabilities of each of these bleed events may depend on the distribution of the severity of bleed events for the selected treatment option. If the patient is predicted to suffer from a fatal event **1414**, a subsequent health state corresponding to this event would be Health State 31, death **3100**. If the patient is predicted to suffer from intra-cranial hemorrhage **1416**, a subsequent health state corresponding to this event would be Health State 12 (step **1200**).

[0181] If the patient is predicted to suffer from a major non-cranial hemorrhage **1418**, the simulation may predict that the patient could be permanently discontinued from the existing course of treatment **1422**, which is the administration of the selected treatment

option, and a subsequent health state corresponding to the bleed event and the new course of treatment would be Health State 16 (step **1600**). The patient may be permanently discontinued from the existing course of treatment **1422** at any rate. Preferably, the patient may be permanently discontinued from the existing course of treatment **1422** at a probability of 25%. Alternatively, the patient may remain under the selected treatment option **1424**, but may be temporarily discontinued from the existing course of treatment **1426** by a period of three months or 90 days. The patient may be temporarily discontinued from the existing course of treatment **1426** at any rate. Preferably, the patient may be temporarily discontinued from the existing course of treatment **1426** when the major non-cranial hemorrhage are gastrointestinal, which may, for example, be at a probability of 89.9%. If the patient is predicted to suffer from a major non-cranial hemorrhage **1418** and the simulation predicts that the patient is temporarily discontinued from the existing course of treatment **1426**, a subsequent health state corresponding to the bleed event and the new course of treatment would be Health State 15 (step **1500**). If the patient is predicted to suffer from a major non-cranial hemorrhage **1418** and the simulation predicts that the patient continues the existing course of treatment **1428**, a subsequent health state corresponding to the bleed event and the new course of treatment would be Health State 15 (step **1500**).

[0182] If the patient is predicted to suffer from a minor hemorrhage **1420**, a subsequent health state would remain as Health State 3 (step **300**). Similarly, if the patient is predicted not to experience an adverse event **1408**, the simulation may predict that a subsequent health state would also remain as Health State 3 (step **300**).

Health State 15 (step **1500**)

[0183] In Health State 15 (step **1500**), the patient is predicted to have a moderate to severe ischemic stroke and major non-cranial hemorrhage and under a course of treatment that comprises administration of a particular treatment option to the patient. For each iteration of the simulation, there is a predicted probability that the patient may die from adverse events unrelated to stroke and/or bleed events **1502**, which includes adjustments to reflect an increased likelihood of death by other causes following a stroke, as well as the relative risk of death not caused by stroke or bleed events for a patient in NVAF under a particular treatment option (e.g., 1.3 for aspirin and 1.3 for warfarin). An exemplary increase of the relative risk of death by adverse events unrelated to stroke and/or bleed event after a patient suffers from a stroke may be 2.3. If the patient suffers from an adverse events

unrelated to stroke and/or bleed events, a subsequent health state corresponding to this event would be Health State 31, death **3100**.

[0184] The patient may also experience stroke events **1504**, bleed events **1506**, or no adverse events **1508**. The probability of the patient experiencing stroke events **1404** may be determined using the baseline risk profile generated by a stroke index, such as, for example, the CHADS₂ scores and probabilities, which may be adjusted by the increase in relative risk of recurrent strokes and the relative risk for the selected treatment option as compared to aspirin. The relative risk of recurrent stroke may, for example, be at a rate of 2. If the patient is predicted to suffer from a stroke event **1504**, the patient may experience a fatal event **1510** or a moderate to severe ischemic stroke **1512**. The probabilities of each of these stroke events may depend on the distribution of the severity of stroke events for the selected treatment option. For example, for a patient receiving warfarin, 8.2% of the stroke events are predicted to result in a fatal event **1510**, the remainder of the stroke events is predicted to result in moderate to severe ischemic stroke **1512**. If the patient is predicted to suffer from a fatal event **1510**, a subsequent health state corresponding to this event would be Health State 31, death **3100**. If the patient is predicted to suffer from moderate to severe ischemic stroke **1512**, a subsequent health state corresponding to this event would be Health State 6 (step **600**), which reflects the patient having suffered from a recurrent stroke, after having already experienced a moderate to severe ischemic stroke, which is one of the existing conditions represented by Health State 15 (step **1500**).

[0185] The probability of the patient experiencing bleed events **1506** may be determined using the baseline risk profile generated by a bleed index, such as, for example, the ATRIA scores and probabilities, which may be adjusted by the increase in relative risk of recurrent bleeds and the relative risk for the selected treatment option as compared to warfarin. The relative risk of recurrent bleed may, for example, be at a rate of 1.5. If the patient is predicted to suffer from a bleed event **1506**, the patient may experience a fatal event **1514**, intra-cranial hemorrhage **1516**, major non-cranial hemorrhage **1518**, or minor hemorrhage **1520**. The probabilities of each of these bleed events may depend on the distribution of the severity of bleed events for the selected treatment option. If the patient is predicted to suffer from a fatal event **1514**, a subsequent health state corresponding to this event would be Health State 31, death **3100**. If the patient is predicted to suffer from intra-

cranial hemorrhage **1516**, a subsequent health state corresponding to this event would be Health State 12 (step **1200**).

[0186] If the patient is predicted to suffer from a major non-cranial hemorrhage **1518**, the simulation may predict that the patient could be permanently discontinued from the existing course of treatment **1522**, which is the administration of the selected treatment option, and a subsequent health state corresponding to the bleed event and the new course of treatment would be Health State 16 (step **1600**). The patient may be permanently discontinued from the existing course of treatment **1522** at any rate. Preferably, the patient may be permanently discontinued from the existing course of treatment **1522** at a probability of 25%. Alternatively, the patient may remain under the selected treatment option **1524**, but may be temporarily discontinued from the existing course of treatment **1526** by a period of three months or 90 days. The patient may be temporarily discontinued from the existing course of treatment **1526** at any rate. Preferably, the patient may be temporarily discontinued from the existing course of treatment **1526** when the major non-cranial hemorrhage are gastrointestinal, which may, for example, be at a probability of 89.9%. If the patient is predicted to suffer from a major non-cranial hemorrhage **1518** and the simulation predicts that the patient is temporarily discontinued from the existing course of treatment **1526**, a subsequent health state corresponding to the bleed event and the new course of treatment would be Health State 15 (step **1500**). If the patient is predicted to suffer from a major non-cranial hemorrhage **1518** and the simulation predicts that the patient continues the existing course of treatment **1528**, a subsequent health state corresponding to the bleed event and the new course of treatment would be Health State 15 (step **1500**).

[0187] If the patient is predicted to suffer from a minor hemorrhage **1520**, a subsequent health state would remain as Health State 3 (step **300**). Similarly, if the patient is predicted not to experience an adverse event **1508**, the simulation may predict that a subsequent health state would also remain as Health State 3 (step **300**).

Health State 16 (step 1600)

[0188] In Health State 16 (step **1600**), the patient is predicted to have a moderate to severe ischemic stroke and a major non-cranial hemorrhage and is permanently discontinued from the treatment option. For each iteration of the simulation, there is a predicted probability that the patient may die from adverse events unrelated to stroke and/or bleed

events **1602**, which includes adjustments to reflect an increased likelihood of death by other causes following a stroke, as well as the relative risk of death not caused by stroke or bleed events for a patient in NVAf under a particular treatment option (e.g., 1.3 for aspirin and 1.3 for warfarin). An exemplary increase of the relative risk of death by adverse events unrelated to stroke and/or bleed event after a patient suffers from a stroke may be 2.3. If the patient suffers from an adverse events unrelated to stroke and/or bleed events, a subsequent health state corresponding to this event would be Health State 31, death **3100**.

[0189] The patient may also experience stroke events **1604**, bleed events **1606**, or no adverse events **1608**. The probability of the patient experiencing stroke events **1604** may be determined using the baseline risk profile generated by a stroke index, such as, for example, the CHADS₂ scores and probabilities, which may be adjusted by the increase in relative risk of recurrent strokes and the relative risk for the selected treatment option as compared to aspirin. The relative risk of recurrent stroke may, for example, be at a rate of 2. If the patient is predicted to suffer from a stroke event **1604**, the patient may experience a fatal event **1610** or a moderate to severe ischemic stroke **1612**. The probabilities of each of these stroke events may depend on the distribution of the severity of stroke events for the selected treatment option. For example, for a patient receiving warfarin, 8.2% of the stroke events are predicted to result in a fatal event **1610**, the remainder of the stroke events is predicted to result in moderate to severe ischemic stroke **1612**. If the patient is predicted to suffer from a fatal event **1610**, a subsequent health state corresponding to this event would be Health State 31, death **3100**. If the patient is predicted to suffer from moderate to severe ischemic stroke **1612**, a subsequent health state corresponding to this event would be Health State 6 (step **2200**), which reflects the patient having suffered from a recurrent stroke, after having already experienced a moderate to severe ischemic stroke, which is one of the existing conditions represented by Health State 16 (step **1600**).

[0190] The probability of the patient experiencing bleed events **1606** may be determined using the baseline risk profile generated by a bleed index, such as, for example, the ATRIA scores and probabilities, which may be adjusted by the increase in relative risk of recurrent bleeds and the relative risk for the selected treatment option as compared to warfarin. The relative risk of recurrent bleed may, for example, be at a rate of 1.5. If the patient is predicted to suffer from a bleed event **1606**, the patient may experience a fatal event **1614**, intra-cranial hemorrhage **1616**, major non-cranial hemorrhage **1618**, or minor

hemorrhage **1620**. The probabilities of each of these bleed events may depend on the distribution of the severity of bleed events for the selected treatment option. If the patient is predicted to suffer from a fatal event **1614**, a subsequent health state corresponding to this event would be Health State 31, death **3100**. If the patient is predicted to suffer from intra-cranial hemorrhage **1616**, a subsequent health state corresponding to this event would be Health State 22 (step **2200**).

[0191] If the patient is predicted to suffer from a major non-cranial hemorrhage **1618**, the simulation may predict that the patient could be permanently discontinued from the existing course of treatment **1622**, and a subsequent health state corresponding to the bleed event and the new course of treatment would be Health State 16 (step **1600**). The patient may be permanently discontinued from the existing course of treatment **1622** at any rate. Preferably, the patient may be permanently discontinued from the existing course of treatment **1622** at a probability of 25%. Alternatively, the patient may remain under the selected treatment option **1624**, but may be temporarily discontinued from the existing course of treatment **1626** by a period of three months or 90 days. The patient may be temporarily discontinued from the existing course of treatment **1626** at any rate. Preferably, the patient may be temporarily discontinued from the existing course of treatment **1626** when the major non-cranial hemorrhage is gastrointestinal, which may, for example, be at a probability of 89.9%. If the patient is predicted to suffer from a major non-cranial hemorrhage **1618** and the simulation predicts that the patient is temporarily discontinued from the existing course of treatment **1626**, a subsequent health state may remain as Health State 16 (step **1600**). If the patient is predicted to suffer from a major non-cranial hemorrhage **1618** and the simulation predicts that the patient continues the existing course of treatment **1628**, a subsequent health state may remain as Health State 16 (step **1600**). If the patient is predicted to suffer from a minor hemorrhage **1620**, a subsequent health state would remain as Health State 16 (step **1600**). Similarly, if the patient is predicted not to experience an adverse event **1608**, the simulation may predict that a subsequent health state would also remain as Health State 16 (step **1600**).

Health State 17 (step **1700**)

[0192] In Health State 17 (step **1700**), the patient is predicted to have a mild ischemic stroke and a major non-cranial hemorrhage and is temporarily discontinued from the treatment option. For each iteration of the simulation, there is a predicted probability that the

patient may die from adverse events unrelated to stroke and/or bleed events **1702**, which includes adjustments to reflect an increased likelihood of death by other causes following a stroke, as well as the relative risk of death not caused by stroke or bleed events for a patient in NVAf under a particular treatment option (e.g., 1.3 for aspirin and 1.3 for warfarin). An exemplary increase of the relative risk of death by adverse events unrelated to stroke and/or bleed event after a patient suffers from a stroke may be 2.3. If the patient suffers from an adverse events unrelated to stroke and/or bleed events, a subsequent health state corresponding to this event would be Health State 31, death **3100**.

[0193] The patient may also experience stroke events **1704**, bleed events **1706**, or no adverse events **1708**. The probability of the patient experiencing stroke events **1704** may be determined using the baseline risk profile generated by a stroke index, such as, for example, the CHADS₂ scores and probabilities, which may be adjusted by the increase in relative risk of recurrent strokes and the relative risk for the selected treatment option as compared to aspirin. The relative risk of recurrent stroke may, for example, be at a rate of 2. If the patient is predicted to suffer from a stroke event **1704**, the patient may experience a fatal event **1710**, a moderate to severe ischemic stroke **1712**, or a mild ischemic stroke **1714**. The probabilities of each of these stroke events may depend on the distribution of the severity of stroke events for the selected treatment option. For example, for a patient receiving warfarin, 8.2% of the stroke events are predicted to result in a fatal event **1710**, 40.2% of the stroke events are predicted to result in moderate to severe ischemic stroke **1712**, and the remainder of the stroke events is predicted to result in mild ischemic stroke **1714**. If the patient is predicted to suffer from a fatal event **1710**, a subsequent health state corresponding to this event would be Health State 31, death **3100**. If the patient is predicted to suffer from moderate to severe ischemic stroke **1712**, a subsequent health state corresponding to this event would be Health State 20 (step **2000**). If the patient is predicted to suffer from mild ischemic stroke **1714**, a subsequent health state corresponding to this event would be Health State 20 (step **2000**), after having already experienced a mild ischemic stroke, which is one of the existing conditions represented by Health State 17 (step **1700**).

[0194] The probability of the patient experiencing bleed events **1706** may be determined using the baseline risk profile generated by a bleed index, such as, for example, the ATRIA scores and probabilities, which may be adjusted by the increase in relative risk of recurrent bleeds and the relative risk for the selected treatment option as compared to

warfarin. The relative risk of recurrent bleed may, for example, be at a rate of 1.5. If the patient is predicted to suffer from a bleed event **1706**, the patient may experience a fatal event **1716**, intra-cranial hemorrhage **1718**, major non-cranial hemorrhage **1720**, or minor hemorrhage **1722**. The probabilities of each of these bleed events may depend on the distribution of the severity of bleed events for the selected treatment option. If the patient is predicted to suffer from a fatal event **1716**, a subsequent health state corresponding to this event would be Health State 31, death **3100**. If the patient is predicted to suffer from intra-cranial hemorrhage **1718**, a subsequent health state corresponding to this event would be Health State 12 (step **1200**).

[0195] If the patient is predicted to suffer from a major non-cranial hemorrhage **1720**, the simulation may predict that the patient could be permanently discontinued from the existing course of treatment **1724**, which is the administration of the selected treatment option, and a subsequent health state corresponding to the bleed event and the new course of treatment would be Health State 19 (step **1900**). The patient may be permanently discontinued from the existing course of treatment **1724** at any rate. Preferably, the patient may be permanently discontinued from the existing course of treatment **1724** at a probability of 25%. Alternatively, the patient may remain under the selected treatment option **1726**, but may be temporarily discontinued from the existing course of treatment **1728** by a period of three months or 90 days. The patient may be temporarily discontinued from the existing course of treatment **1728** at any rate. Preferably, the patient may be temporarily discontinued from the existing course of treatment **1728** when the major non-cranial hemorrhage are gastrointestinal, which may, for example, be at a probability of 89.9%. If the patient is predicted to suffer from a major non-cranial hemorrhage **1720** and the simulation predicts that the patient is temporarily discontinued from the existing course of treatment **1728**, a subsequent health state corresponding to the bleed event and the new course of treatment would remain as Health State 17 (step **1700**). If the patient is predicted to suffer from a major non-cranial hemorrhage **1720** and the simulation predicts that the patient continues the existing course of treatment **1730**, a subsequent health state would be Health State 18 (step **1800**) to reflect the non-GI nature of the bleed event.

[0196] If the patient is predicted to suffer from a minor hemorrhage **1722**, a subsequent health state would also be Health State 18 (step **1800**). Similarly, if the patient is

predicted not to experience an adverse event **1708**, the simulation may predict that a subsequent health state would also remain as Health State 18 (step **1800**).

Health State 18 (step **1800**)

[0197] In Health State 18 (step **1800**), the patient is predicted to have a mild ischemic stroke and a prior major non-cranial hemorrhage and under a course of treatment that comprises administration of a particular treatment option to the patient. For each iteration of the simulation, there is a predicted probability that the patient may die from adverse events unrelated to stroke and/or bleed events **1802**, which includes adjustments to reflect an increased likelihood of death by other causes following a stroke, as well as the relative risk of death not caused by stroke or bleed events for a patient in NVAf under a particular treatment option (e.g., 1.3 for aspirin and 1.3 for warfarin). An exemplary increase of the relative risk of death by adverse events unrelated to stroke and/or bleed event after a patient suffers from a stroke may be 2.3. If the patient suffers from an adverse events unrelated to stroke and/or bleed events, a subsequent health state corresponding to this event would be Health State 31, death **3100**.

[0198] The patient may also experience stroke events **1804**, bleed events **1806**, or no adverse events **1808**. The probability of the patient experiencing stroke events **1804** may be determined using the baseline risk profile generated by a stroke index, such as, for example, the CHADS₂ scores and probabilities, which may be adjusted by the increase in relative risk of recurrent strokes and the relative risk for the selected treatment option as compared to aspirin. The relative risk of recurrent stroke may, for example, be at a rate of 2. If the patient is predicted to suffer from a stroke event **1804**, the patient may experience a fatal event **1810**, a moderate to severe ischemic stroke **1812**, or a mild ischemic stroke **1814**. The probabilities of each of these stroke events may depend on the distribution of the severity of stroke events for the selected treatment option. For example, for a patient receiving warfarin, 8.2% of the stroke events are predicted to result in a fatal event **1810**, 40.2% of the stroke events are predicted to result in moderate to severe ischemic stroke **1812**, and the remainder of the stroke events is predicted to result in mild ischemic stroke **1814**. If the patient is predicted to suffer from a fatal event **1810**, a subsequent health state corresponding to this event would be Health State 31, death **3100**. If the patient is predicted to suffer from moderate to severe ischemic stroke **1812**, a subsequent health state corresponding to this event would be Health State 20 (step **2000**). If the patient is predicted to suffer from mild ischemic stroke **1814**, a

subsequent health state corresponding to this event would be Health State 20 (step **2000**), after having already experienced a mild ischemic stroke, which is one of the existing conditions represented by Health State 18 (step **1800**).

[0199] The probability of the patient experiencing bleed events **1806** may be determined using the baseline risk profile generated by a bleed index, such as, for example, the ATRIA scores and probabilities, which may be adjusted by the increase in relative risk of recurrent bleeds and the relative risk for the selected treatment option as compared to warfarin. The relative risk of recurrent bleed may, for example, be at a rate of 1.5. If the patient is predicted to suffer from a bleed event **1806**, the patient may experience a fatal event **1816**, intra-cranial hemorrhage **1818**, major non-cranial hemorrhage **1820**, or minor hemorrhage **1822**. The probabilities of each of these bleed events may depend on the distribution of the severity of bleed events for the selected treatment option. If the patient is predicted to suffer from a fatal event **1816**, a subsequent health state corresponding to this event would be Health State 31, death **3100**. If the patient is predicted to suffer from intra-cranial hemorrhage **1818**, a subsequent health state corresponding to this event would be Health State 12 (step **1200**).

[0200] If the patient is predicted to suffer from a major non-cranial hemorrhage **1820**, the simulation may predict that the patient could be permanently discontinued from the existing course of treatment **1824**, which is the administration of the selected treatment option, and a subsequent health state corresponding to the bleed event and the new course of treatment would be Health State 16 (step **1600**). The patient may be permanently discontinued from the existing course of treatment **1824** at any rate. Preferably, the patient may be permanently discontinued from the existing course of treatment **1824** at a probability of 25%. Alternatively, the patient may remain under the selected treatment option **1826**, but may be temporarily discontinued from the existing course of treatment **1828** by a period of three months or 90 days. The patient may be temporarily discontinued from the existing course of treatment **1828** at any rate. Preferably, the patient may be temporarily discontinued from the existing course of treatment **1828** when the major non-cranial hemorrhage is gastrointestinal, which may, for example, be at a probability of 89.9%. If the patient is predicted to suffer from a major non-cranial hemorrhage **1820** and the simulation predicts that the patient is temporarily discontinued from the existing course of treatment **1828**, a subsequent health state corresponding to the bleed event and the new course of treatment

would remain as Health State 17 (step **1700**). If the patient is predicted to suffer from a major non-cranial hemorrhage **1820** and the simulation predicts that the patient continues the existing course of treatment **1830**, a subsequent health state would be Health State 18 (step **1800**) to reflect the non-GI nature of the bleed event.

[0201] If the patient is predicted to suffer from a minor hemorrhage **1822**, a subsequent health state would also be Health State 18 (step **1800**). Similarly, if the patient is predicted not to experience an adverse event **1808**, the simulation may predict that a subsequent health state would also remain as Health State 18 (step **1800**).

Health State 19 (step **1900**)

[0202] In Health State 19 (step **1900**), the patient is predicted to have a mild ischemic stroke and a major non-cranial hemorrhage and is permanently discontinued from the treatment option. For each iteration of the simulation, there is a predicted probability that the patient may die from adverse events unrelated to stroke and/or bleed events **1902**, which includes adjustments to reflect an increased likelihood of death by other causes following a stroke, as well as the relative risk of death not caused by stroke or bleed events for a patient in NVAf under a particular treatment option (e.g., 1.3 for aspirin and 1.3 for warfarin). An exemplary increase of the relative risk of death by adverse events unrelated to stroke and/or bleed event after a patient suffers from a stroke may be 2.3. If the patient suffers from an adverse events unrelated to stroke and/or bleed events, a subsequent health state corresponding to this event would be Health State 31, death **3100**.

[0203] The patient may also experience stroke events **1904**, bleed events **1906**, or no adverse events **1908**. The probability of the patient experiencing stroke events **1904** may be determined using the baseline risk profile generated by a stroke index, such as, for example, the CHADS₂ scores and probabilities, which may be adjusted by the increase in relative risk of recurrent strokes and the relative risk for the selected treatment option as compared to aspirin. The relative risk of recurrent stroke may, for example, be at a rate of 2. If the patient is predicted to suffer from a stroke event **1904**, the patient may experience a fatal event **1910**, a moderate to severe ischemic stroke **1912**, or a mild ischemic stroke **1914**. The probabilities of each of these stroke events may depend on the distribution of the severity of stroke events for the selected treatment option. For example, for a patient receiving warfarin, 8.2% of the stroke events are predicted to result in a fatal event **1910**, 40.2% of the stroke events are

predicted to result in moderate to severe ischemic stroke **1912**, and the remainder of the stroke events is predicted to result in mild ischemic stroke **1914**. If the patient is predicted to suffer from a fatal event **1910**, a subsequent health state corresponding to this event would be Health State 31, death **3100**. If the patient is predicted to suffer from moderate to severe ischemic stroke **1912**, a subsequent health state corresponding to this event would be Health State 22 (step **2200**). If the patient is predicted to suffer from mild ischemic stroke **1914**, a subsequent health state corresponding to this event would be Health State 22 (step **2200**), after having already experienced a mild ischemic stroke, which is one of the existing conditions represented by Health State 19 (step **1900**).

[0204] The probability of the patient experiencing bleed events **1906** may be determined using the baseline risk profile generated by a bleed index, such as, for example, the ATRIA scores and probabilities, which may be adjusted by the increase in relative risk of recurrent bleeds and the relative risk for the selected treatment option as compared to warfarin. The relative risk of recurrent bleed may, for example, be at a rate of 1.5. If the patient is predicted to suffer from a bleed event **1906**, the patient may experience a fatal event **1916**, intra-cranial hemorrhage **1918**, major non-cranial hemorrhage **1920**, or minor hemorrhage **1922**. The probabilities of each of these bleed events may depend on the distribution of the severity of bleed events for the selected treatment option. If the patient is predicted to suffer from a fatal event **1916**, a subsequent health state corresponding to this event would be Health State 31, death **3100**. If the patient is predicted to suffer from intra-cranial hemorrhage **1918**, a subsequent health state corresponding to this event would be Health State 12 (step **1200**).

[0205] If the patient is predicted to suffer from a major non-cranial hemorrhage **1920**, the simulation may predict that the patient could be permanently discontinued from the existing course of treatment **1924**, which is the administration of the selected treatment option, and a subsequent health state would remain as Health State 19 (step **1900**). The patient may be permanently discontinued from the existing course of treatment **1924** at any rate. Preferably, the patient may be permanently discontinued from the existing course of treatment **1924** at a probability of 25%. Alternatively, the patient may remain under the selected treatment option **1926**, but may be temporarily discontinued from the existing course of treatment **1928** by a period of three months or 90 days. The patient may be temporarily discontinued from the existing course of treatment **1928** at any rate. Preferably, the patient

may be temporarily discontinued from the existing course of treatment **1928** when the major non-cranial hemorrhage are gastrointestinal, which may, for example, be at a probability of 89.9%.

[0206] If the patient is predicted to suffer from a major non-cranial hemorrhage **1920** and the simulation predicts that the patient is temporarily discontinued from the existing course of treatment **1928**, a subsequent health state would also remain as Health State 19 (step **1900**). If the patient is predicted to suffer from a major non-cranial hemorrhage **1920** and the simulation predicts that the patient continues the existing course of treatment **1930**, a subsequent health state would also be Health State 19 (step **1900**). If the patient is predicted to suffer from a minor hemorrhage **1922**, a subsequent health state would be Health State 19 (step **1900**). Similarly, if the patient is predicted not to experience an adverse event **1908**, the simulation may predict that a subsequent health state would also remain as Health State 19 (step **1900**).

Health State 20 (step 2000)

[0207] In Health State 20 (step **2000**), the patient is predicted to have recurrent stroke and a prior major non-cranial hemorrhage and under a course of treatment that comprises administration of a particular treatment option to the patient. For each iteration of the simulation, there is a predicted probability that the patient may die from adverse events unrelated to stroke and/or bleed events **2002**, which includes adjustments to reflect an increased likelihood of death by other causes following a stroke, as well as the relative risk of death not caused by stroke or bleed events for a patient in NVAf under a particular treatment option (e.g., 1.3 for aspirin and 1.3 for warfarin). An exemplary increase of the relative risk of death by adverse events unrelated to stroke and/or bleed event after a patient suffers from a stroke may be 2.3. If the patient suffers from an adverse events unrelated to stroke and/or bleed events, a subsequent health state corresponding to this event would be Health State 31, death **3100**.

[0208] The patient may also experience stroke events **2004**, bleed events **2006**, or no adverse events **2008**. The probability of the patient experiencing stroke events **2004** may be determined using the baseline risk profile generated by a stroke index, such as, for example, the CHADS₂ scores and probabilities, which may be adjusted by the increase in relative risk of recurrent strokes and the relative risk for the selected treatment option as compared to

aspirin. The relative risk of recurrent stroke may, for example, be at a rate of 2. If the patient is predicted to suffer from a stroke event **2004**, the patient may experience a fatal event **2010**, a moderate to severe ischemic stroke **2012**, or a mild ischemic stroke **2014**. The probabilities of each of these stroke events may depend on the distribution of the severity of stroke events for the selected treatment option. If the patient is predicted to suffer from a fatal event **2010**, a subsequent health state corresponding to this event would be Health State 31, death **3100**. If the patient is predicted to suffer from moderate to severe ischemic stroke **2012** or mild ischemic stroke **2014**, the simulation also predicts that the patient will die (Health State 31, step **3100**) from such a stroke event because of the patient's severely diminished health in this health state, the patient is not likely to survive an additional stroke.

[0209] The probability of the patient experiencing bleed events **2006** may be determined using the baseline risk profile generated by a bleed index, such as, for example, the ATRIA scores and probabilities, which may be adjusted by the increase in relative risk of recurrent bleeds and the relative risk for the selected treatment option as compared to warfarin. The relative risk of recurrent bleed may, for example, be at a rate of 1.5. If the patient is predicted to suffer from a bleed event **2006**, the patient may experience a fatal event **2016**, intra-cranial hemorrhage **2018**, major non-cranial hemorrhage **2020**, or minor hemorrhage **2022**. The probabilities of each of these bleed events may depend on the distribution of the severity of bleed events for the selected treatment option. If the patient is predicted to suffer from a fatal event **2016**, a subsequent health state corresponding to this event would be Health State 31, death **3100**. If the patient is predicted to suffer from intra-cranial hemorrhage **2018**, the simulation also predicts that the patient will die (Health State 31, step **3100**) from such a bleed event because of the patient's severely diminished health in this health state, the patient is not likely to survive an intra-cranial hemorrhage.

[0210] If the patient is predicted to suffer from a major non-cranial hemorrhage **2020**, the simulation may predict that the patient could be permanently discontinued from the existing course of treatment **2024**, and a subsequent health state corresponding to the bleed event and the new course of treatment would be Health State 22 (step **2200**). The patient may be permanently discontinued from the existing course of treatment **2024** at any rate. Preferably, the patient may be permanently discontinued from the existing course of treatment **2024** at a probability of 25%. Alternatively, the patient may remain under the selected treatment option **2026**, but may be temporarily discontinued from the existing course

of treatment **2028** by a period of three months or 90 days. The patient may be temporarily discontinued from the existing course of treatment **2028** at any rate. Preferably, the patient may be temporarily discontinued from the existing course of treatment **2028** when the major non-cranial hemorrhage are gastrointestinal, which may, for example, be at a probability of 89.9%. If the patient is predicted to suffer from a major non-cranial hemorrhage **2020** and the simulation predicts that the patient is temporarily discontinued from the existing course of treatment **2028**, a subsequent health state corresponding to the bleed event and the new course of treatment would be Health State 21 (step **2100**). If the patient is predicted to suffer from a major non-cranial hemorrhage **2020** and the simulation predicts that the patient continues the existing course of treatment **2030**, a subsequent health state would remain as Health State 20 (step **2000**) to reflect the non-GI nature of the bleed event.

[0211] If the patient is predicted to suffer from a minor hemorrhage **2022**, a subsequent health state would be Health State 6 (step **600**). Similarly, if the patient is predicted not to experience an adverse event **2008**, the simulation may predict that a subsequent health state would remain as Health State 20 (step **2000**).

Health State 21 (step **2100**)

[0212] In Health State 21 (step **2100**), the patient is predicted to have recurrent stroke and a major non-cranial hemorrhage and is temporarily discontinued from the treatment option. For each iteration of the simulation, there is a predicted probability that the patient may die from adverse events unrelated to stroke and/or bleed events **2102**, which includes adjustments to reflect an increased likelihood of death by other causes following a stroke, as well as the relative risk of death not caused by stroke or bleed events for a patient in NVAf under a particular treatment option (e.g., 1.3 for aspirin and 1.3 for warfarin). An exemplary increase of the relative risk of death by adverse events unrelated to stroke and/or bleed event after a patient suffers from a stroke may be 2.3. If the patient suffers from an adverse events unrelated to stroke and/or bleed events, a subsequent health state corresponding to this event would be Health State 31, death **3100**.

[0213] The patient may also experience stroke events **2104**, bleed events **2106**, or no adverse events **2108**. The probability of the patient experiencing stroke events **2104** may be determined using the baseline risk profile generated by a stroke index, such as, for example, the CHADS₂ scores and probabilities, which may be adjusted by the increase in relative risk

of recurrent strokes and the relative risk for the selected treatment option as compared to aspirin. The relative risk of recurrent stroke may, for example, be at a rate of 2. If the patient is predicted to suffer from a stroke event **2104**, the patient may experience a fatal event **2110**, a moderate to severe ischemic stroke **2112**, or a mild ischemic stroke **2114**. The probabilities of each of these stroke events may depend on the distribution of the severity of stroke events for the selected treatment option. If the patient is predicted to suffer from a fatal event **2110**, a subsequent health state corresponding to this event would be Health State 31, death **3100**. If the patient is predicted to suffer from moderate to severe ischemic stroke **2112** or mild ischemic stroke **2114**, the simulation also predicts that the patient will die (Health State 31, step **3100**) from such a stroke event because of the patient's severely diminished health in this health state, the patient is not likely to survive an additional stroke.

[0214] The probability of the patient experiencing bleed events **2106** may be determined using the baseline risk profile generated by a bleed index, such as, for example, the ATRIA scores and probabilities, which may be adjusted by the increase in relative risk of recurrent bleeds and the relative risk for the selected treatment option as compared to warfarin. The relative risk of recurrent bleed may, for example, be at a rate of 1.5. If the patient is predicted to suffer from a bleed event **2106**, the patient may experience a fatal event **2116**, intra-cranial hemorrhage **2118**, major non-cranial hemorrhage **2120**, or minor hemorrhage **2122**. The probabilities of each of these bleed events may depend on the distribution of the severity of bleed events for the selected treatment option. If the patient is predicted to suffer from a fatal event **2116**, a subsequent health state corresponding to this event would be Health State 31, death **3100**. If the patient is predicted to suffer from intra-cranial hemorrhage **2118**, the simulation also predicts that the patient will die (Health State 31, step **3100**) from such a bleed event because of the patient's severely diminished health in this health state, the patient is not likely to survive an intra-cranial hemorrhage.

[0215] If the patient is predicted to suffer from a major non-cranial hemorrhage **2120**, the simulation may predict that the patient could be permanently discontinued from the existing course of treatment **2124**, and a subsequent health state corresponding to the bleed event and the new course of treatment would be Health State 22 (step **2200**). The patient may be permanently discontinued from the existing course of treatment **2124** at any rate. Preferably, the patient may be permanently discontinued from the existing course of treatment **2124** at a probability of 25%. Alternatively, the patient may remain under the

selected treatment option **2126**, but may be temporarily discontinued from the existing course of treatment **2128** by a period of three months or 90 days. The patient may be temporarily discontinued from the existing course of treatment **2128** at any rate. Preferably, the patient may be temporarily discontinued from the existing course of treatment **2128** when the major non-cranial hemorrhage is gastrointestinal, which may, for example, be at a probability of 89.9%. If the patient is predicted to suffer from a major non-cranial hemorrhage **2120** and the simulation predicts that the patient is temporarily discontinued from the existing course of treatment **2128**, a subsequent health state corresponding to the bleed event and the new course of treatment would be Health State 21 (step **2100**). If the patient is predicted to suffer from a major non-cranial hemorrhage **2120** and the simulation predicts that the patient continues the existing course of treatment **2130**, a subsequent health state would remain as Health State 20 (step **2000**) to reflect the non-GI nature of the bleed event.

[0216] If the patient is predicted to suffer from a minor hemorrhage **2122**, a subsequent health state would be Health State 20 (step **2000**). Similarly, if the patient is predicted not to experience an adverse event **2108**, the simulation may predict that a subsequent health state would be Health State 15 (step **1500**).

Health State 22 (step **2200**)

[0217] In Health State 22 (step **2200**), the patient is predicted to have recurrent stroke and a major non-cranial hemorrhage and is permanently discontinued from the treatment option. For each iteration of the simulation, there is a predicted probability that the patient may die from adverse events unrelated to stroke and/or bleed events **2202**, which includes adjustments to reflect an increased likelihood of death by other causes following a stroke, as well as the relative risk of death not caused by stroke or bleed events for a patient in NVAf under a particular treatment option (e.g., 1.3 for aspirin and 1.3 for warfarin). An exemplary increase of the relative risk of death by adverse events unrelated to stroke and/or bleed event after a patient suffers from a stroke may be 2.3. If the patient suffers from an adverse events unrelated to stroke and/or bleed events, a subsequent health state corresponding to this event would be Health State 31, death **3100**.

[0218] The patient may also experience stroke events **2204**, bleed events **2206**, or no adverse events **2208**. The probability of the patient experiencing stroke events **2204** may be determined using the baseline risk profile generated by a stroke index, such as, for example,

the CHADS₂ scores and probabilities, which may be adjusted by the increase in relative risk of recurrent strokes and the relative risk for the selected treatment option as compared to aspirin. The relative risk of recurrent stroke may, for example, be at a rate of 2. If the patient is predicted to suffer from a stroke event **2204**, the patient may experience a fatal event **2210**, a moderate to severe ischemic stroke **2212**, or a mild ischemic stroke **2214**. The probabilities of each of these stroke events may depend on the distribution of the severity of stroke events for the selected treatment option. If the patient is predicted to suffer from a fatal event **2210**, a subsequent health state corresponding to this event would be Health State 31, death **3100**. If the patient is predicted to suffer from moderate to severe ischemic stroke **2212** or mild ischemic stroke **2214**, the simulation also predicts that the patient will die (Health State 31, step **3100**) from such a stroke event because of the patient's severely diminished health in this health state, the patient is not likely to survive an additional stroke.

[0219] The probability of the patient experiencing bleed events **2206** may be determined using the baseline risk profile generated by a bleed index, such as, for example, the ATRIA scores and probabilities, which may be adjusted by the increase in relative risk of recurrent bleeds and the relative risk for the selected treatment option as compared to warfarin. The relative risk of recurrent bleed may, for example, be at a rate of 1.5. If the patient is predicted to suffer from a bleed event **2206**, the patient may experience a fatal event **2216**, intra-cranial hemorrhage **2218**, major non-cranial hemorrhage **2220**, or minor hemorrhage **2222**. The probabilities of each of these bleed events may depend on the distribution of the severity of bleed events for the selected treatment option. If the patient is predicted to suffer from a fatal event **2216**, a subsequent health state corresponding to this event would be Health State 31, death **3100**. If the patient is predicted to suffer from intra-cranial hemorrhage **2218**, the simulation also predicts that the patient will die (Health State 31, step **3100**) from such a bleed event because of the patient's severely diminished health in this health state.

[0220] If the patient is predicted to suffer from a major non-cranial hemorrhage **2220** and the simulation predicts that the patient is temporarily discontinued from the existing course of treatment **2228**, a subsequent health state would also remain as Health State 22 (step **2200**). If the patient is predicted to suffer from a major non-cranial hemorrhage **2220** and the simulation predicts that the patient continues the existing course of treatment **2230**, a subsequent health state would also be Health State 22 (step **2200**). If the patient is predicted

to suffer from a minor hemorrhage **2222**, a subsequent health state would be Health State 22 (step **2200**). Similarly, if the patient is predicted not to experience an adverse event **2208**, the simulation may predict that a subsequent health state would also remain as Health State 22 (step **2200**).

Health State 23 (step **2300**)

[0221] In Health State 23 (step **2300**), the patient is predicted to have predicted to have reversible ischemic stroke and a major non-cranial hemorrhage and under a course of treatment that comprises administration of a particular treatment option to the patient. In this particular health state, the patient is not predicted to suffer from an adverse bleed event. For each iteration of the simulation, there is a predicted probability that the patient may die from adverse events unrelated to stroke and/or bleed events **2302**, which includes adjustments to reflect an increased likelihood of death by other causes following a stroke, as well as the relative risk of death not caused by stroke or bleed events for a patient in NVAF under a particular treatment option (e.g., 1.3 for aspirin and 1.3 for warfarin). An exemplary increase of the relative risk of death by adverse events unrelated to stroke and/or bleed event after a patient suffers from a stroke may be 2.3. If the patient suffers from an adverse events unrelated to stroke and/or bleed events, a subsequent health state corresponding to this event would be Health State 31, death **3100**.

[0222] The patient may also experience stroke events **2304**, bleed events **2306**, or no adverse events **2308**. The probability of the patient experiencing stroke events **2304** may be determined using the baseline risk profile generated by a stroke index, such as, for example, the CHADS₂ scores and probabilities, which may be adjusted by the increase in relative risk of recurrent strokes and the relative risk for the selected treatment option as compared to aspirin. The relative risk of recurrent stroke may, for example, be at a rate of 2. If the patient is predicted to suffer from a stroke event **2304**, the patient may experience a fatal event **2310**, a moderate to severe ischemic stroke **2312**, or a mild ischemic stroke **2314**. The probabilities of each of these stroke events may depend on the distribution of the severity of stroke events for the selected treatment option. If the patient is predicted to suffer from a fatal event **2310**, a subsequent health state corresponding to this event would be Health State 31, death **3100**. If the patient is predicted to suffer from moderate to severe ischemic stroke **2312**, a subsequent health state corresponding to this event would be Health State 20 (step **2000**). If the patient is predicted to suffer from mild ischemic stroke **2314**, a subsequent health state

corresponding to this event would be Health State 20 (step **2000**). If the patient is predicted to suffer from reversible ischemic stroke **2316**, a subsequent health state corresponding to this event would be Health State 1 (step **100**).

[0223] The probability of the patient experiencing bleed events **2306** may be determined using the baseline risk profile generated by a bleed index, such as, for example, the ATRIA scores and probabilities, which may be adjusted by the increase in relative risk of recurrent bleeds and the relative risk for the selected treatment option as compared to warfarin. The relative risk of recurrent bleed may, for example, be at a rate of 1.5. If the patient is predicted to suffer from a bleed event **2306**, the patient may experience a fatal event **2318**, intra-cranial hemorrhage **2320**, major non-cranial hemorrhage, or minor hemorrhage **2324**. The probabilities of each of these bleed events may depend on the distribution of the severity of bleed events for the selected treatment option. If the patient is predicted to suffer from a fatal event **2318**, a subsequent health state corresponding to this event would be Health State 31, death **3100**. If the patient is predicted to suffer from intra-cranial hemorrhage **2320**, a subsequent health state corresponding to this event would be Health State 13 (step **1300**).

[0224] If the patient is predicted to suffer from a major non-cranial hemorrhage **2322**, the simulation may predict that the patient could be permanently discontinued from the existing course of treatment **2326**, which is the administration of the selected treatment option, and a subsequent health state corresponding to the bleed event and the new course of treatment would be Health State 25 (step **2500**). The patient may be permanently discontinued from the existing course of treatment **2326** at any rate. Preferably, the patient may be permanently discontinued from the existing course of treatment **2326** at a probability of 25%. Alternatively, the patient may remain under the selected treatment option **2328**, but may be temporarily discontinued from the existing course of treatment **2330** by a period of three months or 90 days. The patient may be temporarily discontinued from the existing course of treatment **2330** at any rate. Preferably, the patient may be temporarily discontinued from the existing course of treatment **2330** when the major non-cranial hemorrhage are gastrointestinal, which may, for example, be at a probability of 89.9%. If the patient is predicted to suffer from a major non-cranial hemorrhage **2322** and the simulation predicts that the patient is temporarily discontinued from the existing course of treatment **2330**, a subsequent health state corresponding to the bleed event and the new course of treatment

would be Health State 25 (step **2500**). If the patient is predicted to suffer from a major non-cranial hemorrhage **2322** and the simulation predicts that the patient continues the existing course of treatment **2332**, a subsequent health state corresponding to the bleed event and the new course of treatment would be Health State 25 (step **2500**).

[0225] If the patient is predicted to suffer from a minor hemorrhage **2324**, the simulation may predict that the patient could be discontinued from the existing course of treatment **2334**, and a subsequent health state corresponding to the bleed event and the new course of treatment would be Health State 30 (step **3000**). If the patient is predicted to suffer from a minor hemorrhage **2324**, the simulation may predict that the patient would continue the existing course of treatment **2336**, and a subsequent health state would remain as Health State 29 (step **2900**). The patient may be discontinued from the existing course of treatment **2334** and/or continue the selected treatment option **2336** at any rate. Moreover, the probability of continuing a treatment option following a minor bleed **2336** may be lower for warfarin than for other treatment options. For example, the probability of continuing warfarin following a minor bleed may be 60% per year, where as the probability of continuing other treatment options (e.g., aspirin, or edoxaban) may be 95% per year.

[0226] If the patient is predicted not to experience an adverse event **2308**, the simulation may predict that the patient may be adherent and continue the existing course of treatment **2340** or non-adherent and discontinue the existing course of treatment **2338**. If the patient is adherent **2340**, then the subsequent health state would remain as Health State 29 (step **2900**). If the patient is non-adherent **2338**, then the subsequent health state would be Health State 30 (step **3000**) to reflect the condition of the patient and the new course of treatment. The patient's adherence and non-adherence to the existing course of treatment may be at any rate. Moreover, the probability of continuing a treatment option **2340** may be lower for warfarin than for other treatment options. For example, the probability of continuing warfarin may be 60% per year, where as the probability of continuing other treatment options (e.g., aspirin, or edoxaban) may be 95% per year. The probabilities applied to the simulation may be adjusted based on the period of life predicted by an iteration of the simulation.

Health State 24 (step **2400**)

[0227] In Health State 24 (step **2400**), the patient is predicted to have predicted to have reversible ischemic stroke and a major non-cranial hemorrhage and is temporarily discontinued from the treatment option. In this particular health state, the patient is not predicted to suffer from an adverse bleed event. For each iteration of the simulation, there is a predicted probability that the patient may die from adverse events unrelated to stroke and/or bleed events **2402**, which includes adjustments to reflect an increased likelihood of death by other causes following a stroke, as well as the relative risk of death not caused by stroke or bleed events for a patient in NVAf under a particular treatment option (e.g., 1.3 for aspirin and 1.3 for warfarin). An exemplary increase of the relative risk of death by adverse events unrelated to stroke and/or bleed event after a patient suffers from a stroke may be 2.3. If the patient suffers from an adverse events unrelated to stroke and/or bleed events, a subsequent health state corresponding to this event would be Health State 31, death **3100**.

[0228] The patient may also experience stroke events **2404**, bleed events **2406**, or no adverse events **2408**. The probability of the patient experiencing stroke events **2404** may be determined using the baseline risk profile generated by a stroke index, such as, for example, the CHADS₂ scores and probabilities, which may be adjusted by the increase in relative risk of recurrent strokes and the relative risk for the selected treatment option as compared to aspirin. The relative risk of recurrent stroke may, for example, be at a rate of 2. If the patient is predicted to suffer from a stroke event **2404**, the patient may experience a fatal event **2410**, a moderate to severe ischemic stroke **2412**, or a mild ischemic stroke **2414**. The probabilities of each of these stroke events may depend on the distribution of the severity of stroke events for the selected treatment option. If the patient is predicted to suffer from a fatal event **2410**, a subsequent health state corresponding to this event would be Health State 31, death **3100**. If the patient is predicted to suffer from moderate to severe ischemic stroke **2412**, a subsequent health state corresponding to this event would be Health State 20 (step **2000**). If the patient is predicted to suffer from mild ischemic stroke **2414**, a subsequent health state corresponding to this event would be Health State 20 (step **2000**). If the patient is predicted to suffer from reversible ischemic stroke **2416**, a subsequent health state corresponding to this event would be Health State 23 (step **2300**).

[0229] The probability of the patient experiencing bleed events **2406** may be determined using the baseline risk profile generated by a bleed index, such as, for example, the ATRIA scores and probabilities, which may be adjusted by the increase in relative risk of

recurrent bleeds and the relative risk for the selected treatment option as compared to warfarin. The relative risk of recurrent bleed may, for example, be at a rate of 1.5. If the patient is predicted to suffer from a bleed event **2406**, the patient may experience a fatal event **2418**, intra-cranial hemorrhage **2420**, major non-cranial hemorrhage, or minor hemorrhage **2424**. The probabilities of each of these bleed events may depend on the distribution of the severity of bleed events for the selected treatment option. If the patient is predicted to suffer from a fatal event **2418**, a subsequent health state corresponding to this event would be Health State 31, death **3100**. If the patient is predicted to suffer from intra-cranial hemorrhage **2420**, a subsequent health state corresponding to this event would be Health State 13 (step **1300**).

[0230] If the patient is predicted to suffer from a major non-cranial hemorrhage **2422**, the simulation may predict that the patient could be permanently discontinued from the existing course of treatment **2426**, which is the administration of the selected treatment option, and a subsequent health state corresponding to the bleed event and the new course of treatment would be Health State 25 (step **2500**). The patient may be permanently discontinued from the existing course of treatment **2426** at any rate. Preferably, the patient may be permanently discontinued from the existing course of treatment **2426** at a probability of 25%. Alternatively, the patient may remain under the selected treatment option **2428**, but may be temporarily discontinued from the existing course of treatment **2430** by a period of three months or 90 days. The patient may be temporarily discontinued from the existing course of treatment **2430** at any rate. Preferably, the patient may be temporarily discontinued from the existing course of treatment **2430** when the major non-cranial hemorrhage are gastrointestinal, which may, for example, be at a probability of 89.9%. If the patient is predicted to suffer from a major non-cranial hemorrhage **2422** and the simulation predicts that the patient is temporarily discontinued from the existing course of treatment **2430**, a subsequent health state corresponding to the bleed event and the new course of treatment would be Health State 25 (step **2500**). If the patient is predicted to suffer from a major non-cranial hemorrhage **2422** and the simulation predicts that the patient continues the existing course of treatment **2432**, a subsequent health state corresponding to the bleed event and the new course of treatment would be Health State 24 (step **2400**).

[0231] If the patient is predicted to suffer from a minor hemorrhage **2424**, the simulation may predict that the patient could be discontinued from the existing course of

treatment **2434**, and a subsequent health state corresponding to the bleed event and the new course of treatment would be Health State 30 (step **3000**). If the patient is predicted to suffer from a minor hemorrhage **2424**, the simulation may predict that the patient would continue the existing course of treatment **2436**, and a subsequent health state would remain as Health State 29 (step **2900**). The patient may be discontinued from the existing course of treatment **2434** and/or continue the selected treatment option **2436** at any rate. Moreover, the probability of continuing a treatment option following a minor bleed **2436** may be lower for warfarin than for other treatment options. For example, the probability of continuing warfarin following a minor bleed may be 60% per year, where as the probability of continuing other treatment options (e.g., aspirin, or edoxaban) may be 95% per year.

[0232] If the patient is predicted not to experience an adverse event **2408**, the simulation may predict that the patient may be adherent and continue the existing course of treatment **2440** or non-adherent and discontinue the existing course of treatment **2438**. If the patient is adherent **2440**, then the subsequent health state would be Health State 29 (step **2900**). If the patient is non-adherent **2438**, then the subsequent health state would be Health State 30 (step **3000**) to reflect the condition of the patient and the new course of treatment. The patient's adherence and non-adherence to the existing course of treatment may be at any rate. Moreover, the probability of continuing a treatment option **2440** may be lower for warfarin than for other treatment options. For example, the probability of continuing warfarin may be 60% per year, where as the probability of continuing other treatment options (e.g., aspirin, or edoxaban) may be 95% per year. The probabilities applied to the simulation may be adjusted based on the period of life predicted by an iteration of the simulation.

Health State 25 (step **2500**)

[0233] In Health State 25 (step **2500**), the patient is predicted to have predicted to have reversible ischemic stroke and a major non-cranial hemorrhage and is permanently discontinued from the treatment option. In this particular health state, the patient is not predicted to suffer from an adverse bleed event. For each iteration of the simulation, there is a predicted probability that the patient may die from adverse events unrelated to stroke and/or bleed events **2502**, which includes adjustments to reflect an increased likelihood of death by other causes following a stroke, as well as the relative risk of death not caused by stroke or bleed events for a patient in NVAf under a particular treatment option (e.g., 1.3 for aspirin and 1.3 for warfarin). An exemplary increase of the relative risk of death by adverse events

unrelated to stroke and/or bleed event after a patient suffers from a stroke may be 2.3. If the patient suffers from an adverse events unrelated to stroke and/or bleed events, a subsequent health state corresponding to this event would be Health State 31, death **3100**.

[0234] The patient may also experience stroke events **2504**, bleed events **2506**, or no adverse events **2508**. The probability of the patient experiencing stroke events **2504** may be determined using the baseline risk profile generated by a stroke index, such as, for example, the CHADS₂ scores and probabilities, which may be adjusted by the increase in relative risk of recurrent strokes and the relative risk for the selected treatment option as compared to aspirin. The relative risk of recurrent stroke may, for example, be at a rate of 2. If the patient is predicted to suffer from a stroke event **2504**, the patient may experience a fatal event **2510**, a moderate to severe ischemic stroke **2512**, or a mild ischemic stroke **2514**. The probabilities of each of these stroke events may depend on the distribution of the severity of stroke events for the selected treatment option. If the patient is predicted to suffer from a fatal event **2510**, a subsequent health state corresponding to this event would be Health State 31, death **3100**. If the patient is predicted to suffer from moderate to severe ischemic stroke **2512**, a subsequent health state corresponding to this event would be Health State 22 (step **2200**). If the patient is predicted to suffer from mild ischemic stroke **2514**, a subsequent health state corresponding to this event would be Health State 22 (step **2200**). If the patient is predicted to suffer from reversible ischemic stroke **2516**, a subsequent health state corresponding to this event would be Health State 25 (step **2500**).

[0235] The probability of the patient experiencing bleed events **2506** may be determined using the baseline risk profile generated by a bleed index, such as, for example, the ATRIA scores and probabilities, which may be adjusted by the increase in relative risk of recurrent bleeds and the relative risk for the selected treatment option as compared to warfarin. The relative risk of recurrent bleed may, for example, be at a rate of 1.5. If the patient is predicted to suffer from a bleed event **2506**, the patient may experience a fatal event **2518**, intra-cranial hemorrhage **2520**, major non-cranial hemorrhage, or minor hemorrhage **2524**. The probabilities of each of these bleed events may depend on the distribution of the severity of bleed events for the selected treatment option. If the patient is predicted to suffer from a fatal event **2518**, a subsequent health state corresponding to this event would be Health State 31, death **3100**. If the patient is predicted to suffer from intra-cranial

hemorrhage **2520**, a subsequent health state corresponding to this event would be Health State 13 (step **1300**).

[0236] If the patient is predicted to suffer from a major non-cranial hemorrhage **2522**, the simulation may predict that the patient could be permanently discontinued from the existing course of treatment **2526**, which is the administration of the selected treatment option, and a subsequent health state corresponding to the bleed event and the new course of treatment would remain as Health State 25 (step **2500**). The patient may be permanently discontinued from the existing course of treatment **2526** at any rate. Preferably, the patient may be permanently discontinued from the existing course of treatment **2526** at a probability of 25%. Alternatively, the patient may remain under the selected treatment option **2528**, but may be temporarily discontinued from the existing course of treatment **2530** by a period of three months or 90 days. The patient may be temporarily discontinued from the existing course of treatment **2530** at any rate. Preferably, the patient may be temporarily discontinued from the existing course of treatment **2530** when the major non-cranial hemorrhage are gastrointestinal, which may, for example, be at a probability of 89.9%. If the patient is predicted to suffer from a major non-cranial hemorrhage **2522** and the simulation predicts that the patient is temporarily discontinued from the existing course of treatment **2530**, a subsequent health state corresponding to the bleed event and the new course of treatment would remain as Health State 25 (step **2500**). If the patient is predicted to suffer from a major non-cranial hemorrhage **2522** and the simulation predicts that the patient continues the existing course of treatment **2532**, a subsequent health state corresponding to the bleed event and the new course of treatment would remain as Health State 25 (step **2500**).

[0237] If the patient is predicted to suffer from a minor hemorrhage **2524**, a subsequent health state would be Health State 30 (step **3000**). Similarly, if the patient is predicted not to experience an adverse event **2508**, the simulation may predict that a subsequent health state would also remain as Health State 30 (step **3000**).

Health State 26 (step **2600**)

[0238] In Health State 26 (step **2600**), the patient is predicted to have a prior reversible ischemic stroke and under a course of treatment comprises administration of a particular treatment option to the patient. In this particular health state, the patient is not predicted to suffer from an adverse bleed event. For each iteration of the simulation, there is

a predicted probability that the patient may die from adverse events unrelated to stroke and/or bleed events **2602**, which includes adjustments to reflect an increased likelihood of death by other causes following a stroke, as well as the relative risk of death not caused by stroke or bleed events for a patient in NVAf under a particular treatment option (e.g., 1.3 for aspirin and 1.3 for warfarin). An exemplary increase of the relative risk of death by adverse events unrelated to stroke and/or bleed event after a patient suffers from a stroke may be 2.3. If the patient suffers from an adverse events unrelated to stroke and/or bleed events, a subsequent health state corresponding to this event would be Health State 31, death **3100**.

[0239] The patient may also experience stroke events **2604**, bleed events **2606**, or no adverse events **2608**. The probability of the patient experiencing stroke events **2604** may be determined using the baseline risk profile generated by a stroke index, such as, for example, the CHADS₂ scores and probabilities, which may be adjusted by the increase in relative risk of recurrent strokes and the relative risk for the selected treatment option as compared to aspirin. The relative risk of recurrent stroke may, for example, be at a rate of 2. If the patient is predicted to suffer from a stroke event **2604**, the patient may experience a fatal event **2610**, a moderate to severe ischemic stroke **2612**, a mild ischemic stroke **2614**, or a reversible ischemic stroke **2616**. The probabilities of each of these stroke events may depend on the distribution of the severity of stroke events for the selected treatment option. For example, for a patient receiving warfarin, 8.2% of the stroke events are predicted to result in a fatal event **2610**, 40.2% of the stroke events are predicted to result in moderate to severe ischemic stroke **2612**, 42.5% of the stroke events are predicted to result in mild ischemic stroke **2614**, and 9.1% of the stroke events are predicted to result in reversible ischemic stroke **2616**. If the patient is predicted to suffer from a fatal event **2610**, a subsequent health state corresponding to this event would be Health State 31, death **3100**. If the patient is predicted to suffer from moderate to severe ischemic stroke **2612**, a subsequent health state corresponding to this event would be Health State 6 (step **600**). If the patient is predicted to suffer from mild ischemic stroke **2614**, a subsequent health state corresponding to this event would be Health State 6 (step **600**). If the patient is predicted to suffer from reversible ischemic stroke **2616**, a subsequent health state corresponding to this event would be Health State 5 (step **500**).

[0240] The probability of the patient experiencing bleed events **2606** may be determined using the baseline risk profile generated by a bleed index, such as, for example,

the ATRIA scores and probabilities, which may be adjusted by the relative risk for the selected treatment option as compared to warfarin. If the patient is predicted to suffer from a bleed event **2606**, the patient may experience a fatal event **2618**, intra-cranial hemorrhage **2620**, major non-cranial hemorrhage **2622**, or minor hemorrhage **2624**. The probabilities of each of these bleed events may depend on the distribution of the severity of bleed events for the selected treatment option. If the patient is predicted to suffer from a fatal event **2618**, a subsequent health state corresponding to this event would be Health State 31, death **3100**. If the patient is predicted to suffer from intra-cranial hemorrhage **2620**, a subsequent health state corresponding to this event would be Health State 13 (step **1300**).

[0241] If the patient is predicted to suffer from a major non-cranial hemorrhage **2622**, the simulation may predict that the patient could be permanently discontinued from the treatment option **2626** (e.g., administration of warfarin or aspirin), and a subsequent health state corresponding to the bleed event would be Health State 25 (step **2500**). The patient may be permanently discontinued from the treatment option **2626** at any rate. Preferably, the patient may be permanently discontinued from the treatment option **2626** at a probability of 25%. Alternatively, the patient may remain under the selected treatment option **2628**, but may be temporarily discontinued **2630** by a period of three months or 90 days. The patient may be temporarily discontinued **2630** at any rate. Preferably, the patient may be temporarily discontinued from the existing course of treatment **2630** when the major non-cranial hemorrhage are gastrointestinal, which may, for example, be at a probability of 89.9%. If the patient is predicted to suffer from a major non-cranial hemorrhage **2622** and the simulation predicts that the patient is temporarily discontinued from the existing course of treatment **2630**, a subsequent health state corresponding to the bleed event and the new course of treatment would be Health State 24 (step **2400**). If the patient is predicted to suffer from a major non-cranial hemorrhage **2622** and the simulation predicts that the patient continues the existing course of treatment **2632**, a subsequent health state corresponding to the bleed event and the new course of treatment would be also be Health State 23 (step **2300**).

[0242] If the patient is predicted to suffer from a minor hemorrhage **2624**, a subsequent health state corresponding would remain as Health State 26 (step **2600**). If the patient is predicted not to experience an adverse event **2608**, a subsequent health state would remain as Health State 26 (step **2600**).

Health State 27 (step **2700**)

[0243] In Health State 27 (step **2700**), the patient is predicted to have a prior major non-cranial hemorrhage and under a course of treatment that comprises administration of a particular treatment option to the patient. In this particular health state, the patient is not predicted to suffer from an adverse stroke event. For each iteration of the simulation, there is a predicted probability that the patient may die from adverse events unrelated to stroke and/or bleed events **2702**, which includes adjustments to reflect an increased likelihood of death by other causes following an intracranial hemorrhage, as well as the relative risk of death not caused by stroke or bleed events for a patient in NVAf under a particular treatment option (e.g., 1.3 for aspirin and 1.3 for warfarin). An exemplary increase of the relative risk of death by adverse events unrelated to stroke and/or bleed event after a patient suffers from a intracranial hemorrhage may be 2.3. If the patient suffers from an adverse events unrelated to stroke and/or bleed events, a subsequent health state corresponding to this event would be Health State 31, death **3100**.

[0244] The patient may also experience stroke events **2704**, bleed events **2706**, or no adverse events **2708**. The probability of the patient experiencing stroke events **2704** may be determined using the baseline risk profile generated by a stroke index, such as, for example, the CHADS₂ scores and probabilities, which may be adjusted by the relative risk for the selected treatment option as compared to aspirin. If the patient is predicted to suffer from a stroke event **2704**, the patient may experience a fatal event **2710**, a moderate to severe ischemic stroke **2712**, a mild ischemic stroke **2714**, or a reversible ischemic stroke **2716**. The probabilities of each of these stroke events may depend on the distribution of the severity of stroke events for the selected treatment option. If the patient is predicted to suffer from a fatal event **2710**, a subsequent health state corresponding to this event would be Health State 31, death **3100**. If the patient is predicted to suffer from moderate to severe ischemic stroke **2712**, a subsequent health state corresponding to this event would be Health State 15 (step **1500**). If the patient is predicted to suffer from mild ischemic stroke **2714**, a subsequent health state corresponding to this event would also be Health State 18 (step **1800**). If the patient is predicted to suffer from reversible ischemic stroke **2716**, a subsequent health state corresponding to this event would be Health State 23 (step **2300**).

[0245] The probability of the patient experiencing bleed events **2706** may be determined using the baseline risk profile generated by a bleed index, such as, for example, the ATRIA scores and probabilities, which may be adjusted by the increase in relative risk of

recurrent bleeds and the relative risk for the selected treatment option as compared to warfarin. The relative risk of recurrent bleed may, for example, be at a rate of 1.5. If the patient is predicted to suffer from a bleed event **2706**, the patient may experience a fatal event **2718**, intra-cranial hemorrhage **2720**, major non-cranial hemorrhage **2722**, or minor hemorrhage **2724**. The probabilities of each of these bleed events may depend on the distribution of the severity of bleed events for the selected treatment option. If the patient is predicted to suffer from a fatal event **2718**, a subsequent health state corresponding to this event would be Health State 31, death **3100**. If the patient is predicted to suffer from intra-cranial hemorrhage **2720**, a subsequent health state corresponding to this event would be Health State 11 (step **1100**).

[0246] If the patient is predicted to suffer from a major non-cranial hemorrhage **2722**, the simulation may predict that the patient could be permanently discontinued from the existing course of treatment **2726**, which is the administration of the selected treatment option, and a subsequent health state corresponding to the bleed event and the new course of treatment would be Health State 10 (step **1000**). The patient may be permanently discontinued from the existing course of treatment **2726** at any rate. Preferably, the patient may be permanently discontinued from the existing course of treatment **2726** at a probability of 25%. Alternatively, the patient may remain under the selected treatment option **2728**, but may be temporarily discontinued from the existing course of treatment **2730** by a period of three months or 90 days. The patient may be temporarily discontinued from the existing course of treatment **2730** at any rate. Preferably, the patient may be temporarily discontinued from the existing course of treatment **2730** when the major non-cranial hemorrhage are gastrointestinal, which may, for example, be at a probability of 89.9%. If the patient is predicted to suffer from a major non-cranial hemorrhage **2722** and the simulation predicts that the patient is temporarily discontinued from the existing course of treatment **2730**, a subsequent health state corresponding to the bleed event and the new course of treatment would be Health State 9 (step **900**). If the patient is predicted to suffer from a major non-cranial hemorrhage **2722** and the simulation predicts that the patient continues the existing course of treatment **2732**, a subsequent health state corresponding to the bleed event would be Health State 9 (step **900**).

[0247] If the patient is predicted to suffer from a minor hemorrhage **2724**, the simulation may predict that the patient could be discontinued from the existing course of

treatment **2734**, and a subsequent health state corresponding to the bleed event and the new course of treatment would be Health State 28 (step **2800**). If the patient is predicted to suffer from a minor hemorrhage **2724**, the simulation may predict that the patient would continue the existing course of treatment **2736**, and a subsequent health state would remain as Health State 27 (step **2700**). The patient may be discontinued from the existing course of treatment **2734** and/or continue the selected treatment option **2736** at any rate. Moreover, the probability of continuing a treatment option following a minor bleed **2736** may be lower for warfarin than for other treatment options. For example, the probability of continuing warfarin following a minor bleed may be 60% per year, where as the probability of continuing other treatment options (e.g., aspirin, or edoxaban) may be 95% per year.

[0248] If the patient is predicted not to experience an adverse event **2708**, the simulation may predict that the patient may be adherent and continue the existing course of treatment **2740** or non-adherent and discontinue the existing course of treatment **2738**. If the patient is adherent **2740**, then the subsequent health state would remain as Health State 27 (step **2700**). If the patient is non-adherent **2738**, then the subsequent health state would be Health State 28 (step **2800**) to reflect the condition of the patient and the new course of treatment. The patient's adherence and non-adherence to the existing course of treatment may be at any rate. Moreover, the probability of continuing a treatment option **2740** may be lower for warfarin than for other treatment options. For example, the probability of continuing warfarin may be 60% per year, where as the probability of continuing other treatment options (e.g., aspirin, or edoxaban) may be 95% per year. The probabilities applied to the simulation may be adjusted based on the period of life predicted by an iteration of the simulation.

Health State 28 (step 2800)

[0249] In Health State 28 (step **2800**), the patient is predicted to have a prior major non-cranial hemorrhage and is permanently discontinued from the treatment option. In this particular health state, the patient is not predicted to suffer from an adverse stroke event. For each iteration of the simulation, there is a predicted probability that the patient may die from adverse events unrelated to stroke and/or bleed events **2802**, which includes adjustments to reflect an increased likelihood of death by other causes following an intracranial hemorrhage, as well as the relative risk of death not caused by stroke or bleed events for a patient in NVAf under a particular treatment option (e.g., 1.3 for aspirin and 1.3 for warfarin). An

exemplary increase of the relative risk of death by adverse events unrelated to stroke and/or bleed event after a patient suffers from a intracranial hemorrhage may be 2.3. If the patient suffers from an adverse events unrelated to stroke and/or bleed events, a subsequent health state corresponding to this event would be Health State 31, death **3100**.

[0250] The patient may also experience stroke events **2804**, bleed events **2806**, or no adverse events **2808**. The probability of the patient experiencing stroke events **2804** may be determined using the baseline risk profile generated by a stroke index, such as, for example, the CHADS₂ scores and probabilities, which may be adjusted by the relative risk for the selected treatment option as compared to aspirin. If the patient is predicted to suffer from a stroke event **2804**, the patient may experience a fatal event **2810**, a moderate to severe ischemic stroke **2812**, a mild ischemic stroke **2814**, or a reversible ischemic stroke **2816**. The probabilities of each of these stroke events may depend on the distribution of the severity of stroke events for the selected treatment option. If the patient is predicted to suffer from a fatal event **2810**, a subsequent health state corresponding to this event would be Health State 31, death **3100**. If the patient is predicted to suffer from moderate to severe ischemic stroke **2812**, a subsequent health state corresponding to this event would be Health State 16 (step **1600**). If the patient is predicted to suffer from mild ischemic stroke **2814**, a subsequent health state corresponding to this event would also be Health State 19 (step **1900**). If the patient is predicted to suffer from reversible ischemic stroke **2816**, a subsequent health state corresponding to this event would be Health State 25 (step **2500**).

[0251] The probability of the patient experiencing bleed events **2806** may be determined using the baseline risk profile generated by a bleed index, such as, for example, the ATRIA scores and probabilities, which may be adjusted by the increase in relative risk of recurrent bleeds and the relative risk for the selected treatment option as compared to warfarin. The relative risk of recurrent bleed may, for example, be at a rate of 1.5. If the patient is predicted to suffer from a bleed event **2806**, the patient may experience a fatal event **2818**, intra-cranial hemorrhage **2820**, major non-cranial hemorrhage **2822**, or minor hemorrhage **2824**. The probabilities of each of these bleed events may depend on the distribution of the severity of bleed events for the selected treatment option. If the patient is predicted to suffer from a fatal event **2818**, a subsequent health state corresponding to this event would be Health State 31, death **3100**. If the patient is predicted to suffer from intra-

cranial hemorrhage **2820**, a subsequent health state corresponding to this event would be Health State 11 (step **1100**).

[0252] If the patient is predicted to suffer from a major non-cranial hemorrhage **2822**, the simulation may predict that the patient could be permanently discontinued from the existing course of treatment **2826**, which is the administration of the selected treatment option, and a subsequent health state corresponding to the bleed event and the new course of treatment would be Health State 10 (step **1000**). The patient may be permanently discontinued from the existing course of treatment **2826** at any rate. Preferably, the patient may be permanently discontinued from the existing course of treatment **2826** at a probability of 25%. Alternatively, the patient may remain under the selected treatment option **2828**, but may be temporarily discontinued from the existing course of treatment **2830** by a period of three months or 90 days. The patient may be temporarily discontinued from the existing course of treatment **2830** at any rate. Preferably, the patient may be temporarily discontinued from the existing course of treatment **2830** when the major non-cranial hemorrhage are gastrointestinal, which may, for example, be at a probability of 89.9%. If the patient is predicted to suffer from a major non-cranial hemorrhage **2822** and the simulation predicts that the patient is temporarily discontinued from the existing course of treatment **2830**, a subsequent health state corresponding to the bleed event and the new course of treatment would be Health State 10 (step **1000**). If the patient is predicted to suffer from a major non-cranial hemorrhage **2822** and the simulation predicts that the patient continues the existing course of treatment **2832**, a subsequent health state corresponding to the bleed event would be Health State 10 (step **1000**).

[0253] If the patient is predicted to suffer from a minor hemorrhage **2824**, a subsequent health state would remain as Health State 28 (step **2800**). Similarly, if the patient is predicted not to experience an adverse event **2808**, the simulation may predict that a subsequent health state would also remain as Health State 28 (step **2800**).

Health State 29 (step **2900**)

[0254] In Health State 29 (step **2900**), the patient is predicted to have predicted to have a prior reversible ischemic stroke and a prior major non-cranial hemorrhage and under a course of treatment that comprises administration of a particular treatment option to the patient. In this particular health state, the patient is not predicted to suffer from an adverse

bleed event. For each iteration of the simulation, there is a predicted probability that the patient may die from adverse events unrelated to stroke and/or bleed events **2902**, which includes adjustments to reflect an increased likelihood of death by other causes following a stroke, as well as the relative risk of death not caused by stroke or bleed events for a patient in NVAf under a particular treatment option (e.g., 1.3 for aspirin and 1.3 for warfarin). An exemplary increase of the relative risk of death by adverse events unrelated to stroke and/or bleed event after a patient suffers from a stroke may be 2.3. If the patient suffers from an adverse events unrelated to stroke and/or bleed events, a subsequent health state corresponding to this event would be Health State 31, death **3100**.

[0255] The patient may also experience stroke events **2904**, bleed events **2906**, or no adverse events **2908**. The probability of the patient experiencing stroke events **2904** may be determined using the baseline risk profile generated by a stroke index, such as, for example, the CHADS₂ scores and probabilities, which may be adjusted by the increase in relative risk of recurrent strokes and the relative risk for the selected treatment option as compared to aspirin. The relative risk of recurrent stroke may, for example, be at a rate of 2. If the patient is predicted to suffer from a stroke event **2904**, the patient may experience a fatal event **2910**, a moderate to severe ischemic stroke **2912**, or a mild ischemic stroke **2914**. The probabilities of each of these stroke events may depend on the distribution of the severity of stroke events for the selected treatment option. If the patient is predicted to suffer from a fatal event **2910**, a subsequent health state corresponding to this event would be Health State 31, death **3100**. If the patient is predicted to suffer from moderate to severe ischemic stroke **2912**, a subsequent health state corresponding to this event would be Health State 20 (step **2000**). If the patient is predicted to suffer from mild ischemic stroke **2914**, a subsequent health state corresponding to this event would be Health State 20 (step **2000**). If the patient is predicted to suffer from reversible ischemic stroke **2916**, a subsequent health state corresponding to this event would be Health State 23 (step **2300**).

[0256] The probability of the patient experiencing bleed events **2906** may be determined using the baseline risk profile generated by a bleed index, such as, for example, the ATRIA scores and probabilities, which may be adjusted by the increase in relative risk of recurrent bleeds and the relative risk for the selected treatment option as compared to warfarin. The relative risk of recurrent bleed may, for example, be at a rate of 1.5. If the patient is predicted to suffer from a bleed event **2906**, the patient may experience a fatal event

2918, intra-cranial hemorrhage **2920**, major non-cranial hemorrhage, or minor hemorrhage **2924**. The probabilities of each of these bleed events may depend on the distribution of the severity of bleed events for the selected treatment option. If the patient is predicted to suffer from a fatal event **2918**, a subsequent health state corresponding to this event would be Health State 31, death **3100**. If the patient is predicted to suffer from intra-cranial hemorrhage **2920**, a subsequent health state corresponding to this event would be Health State 11 (step **1100**).

[0257] If the patient is predicted to suffer from a major non-cranial hemorrhage **2922**, the simulation may predict that the patient could be permanently discontinued from the existing course of treatment **2926**, which is the administration of the selected treatment option, and a subsequent health state corresponding to the bleed event and the new course of treatment would be Health State 25 (step **2500**). The patient may be permanently discontinued from the existing course of treatment **2926** at any rate. Preferably, the patient may be permanently discontinued from the existing course of treatment **2926** at a probability of 25%. Alternatively, the patient may remain under the selected treatment option **2928**, but may be temporarily discontinued from the existing course of treatment **2930** by a period of three months or 90 days. The patient may be temporarily discontinued from the existing course of treatment **2930** at any rate. Preferably, the patient may be temporarily discontinued from the existing course of treatment **2930** when the major non-cranial hemorrhage are gastrointestinal, which may, for example, be at a probability of 89.9%. If the patient is predicted to suffer from a major non-cranial hemorrhage **2922** and the simulation predicts that the patient is temporarily discontinued from the existing course of treatment **2930**, a subsequent health state corresponding to the bleed event and the new course of treatment would be Health State 25 (step **2500**). If the patient is predicted to suffer from a major non-cranial hemorrhage **2922** and the simulation predicts that the patient continues the existing course of treatment **2932**, a subsequent health state corresponding to the bleed event and the new course of treatment would be Health State 25 (step **2500**).

[0258] If the patient is predicted to suffer from a minor hemorrhage **2924**, the simulation may predict that the patient could be discontinued from the existing course of treatment **2934**, and a subsequent health state corresponding to the bleed event and the new course of treatment would be Health State 30 (step **3000**). If the patient is predicted to suffer from a minor hemorrhage **2924**, the simulation may predict that the patient would continue

the existing course of treatment **2936**, and a subsequent health state would remain as Health State 29 (step **2900**). The patient may be discontinued from the existing course of treatment **2934** and/or continue the selected treatment option **2936** at any rate. Moreover, the probability of continuing a treatment option following a minor bleed **2936** may be lower for warfarin than for other treatment options. For example, the probability of continuing warfarin following a minor bleed may be 60% per year, where as the probability of continuing other treatment options (e.g., aspirin, or edoxaban) may be 95% per year.

[0259] If the patient is predicted not to experience an adverse event **2908**, the simulation may predict that the patient may be adherent and continue the existing course of treatment **2940** or non-adherent and discontinue the existing course of treatment **2938**. If the patient is adherent **2940**, then the subsequent health state would remain as Health State 29 (step **2900**). If the patient is non-adherent **2938**, then the subsequent health state would be Health State 30 (step **3000**) to reflect the condition of the patient and the new course of treatment. The patient's adherence and non-adherence to the existing course of treatment may be at any rate. Moreover, the probability of continuing a treatment option **2940** may be lower for warfarin than for other treatment options. For example, the probability of continuing warfarin may be 60% per year, where as the probability of continuing other treatment options (e.g., aspirin, or edoxaban) may be 95% per year. The probabilities applied to the simulation may be adjusted based on the period of life predicted by an iteration of the simulation.

Health State 30 (step **3000**)

[0260] In Health State 30 (step **3000**), the patient is predicted to have predicted to have a prior reversible ischemic stroke and a prior major non-cranial hemorrhage and is permanently discontinued from the treatment option. In this particular health state, the patient is not predicted to suffer from an adverse bleed event. For each iteration of the simulation, there is a predicted probability that the patient may die from adverse events unrelated to stroke and/or bleed events **2502**, which includes adjustments to reflect an increased likelihood of death by other causes following a stroke, as well as the relative risk of death not caused by stroke or bleed events for a patient in NVAf under a particular treatment option (e.g., 1.3 for aspirin and 1.3 for warfarin). An exemplary increase of the relative risk of death by adverse events unrelated to stroke and/or bleed event after a patient suffers from a stroke may be 2.3. If the patient suffers from an adverse events unrelated to stroke and/or

bleed events, a subsequent health state corresponding to this event would be Health State 31, death **3100**.

[0261] The patient may also experience stroke events **3004**, bleed events **3006**, or no adverse events **3008**. The probability of the patient experiencing stroke events **3004** may be determined using the baseline risk profile generated by a stroke index, such as, for example, the CHADS₂ scores and probabilities, which may be adjusted by the increase in relative risk of recurrent strokes and the relative risk for the selected treatment option as compared to aspirin. The relative risk of recurrent stroke may, for example, be at a rate of 2. If the patient is predicted to suffer from a stroke event **3004**, the patient may experience a fatal event **3010**, a moderate to severe ischemic stroke **3012**, or a mild ischemic stroke **3014**. The probabilities of each of these stroke events may depend on the distribution of the severity of stroke events for the selected treatment option. If the patient is predicted to suffer from a fatal event **3010**, a subsequent health state corresponding to this event would be Health State 31, death **3100**. If the patient is predicted to suffer from moderate to severe ischemic stroke **3012**, a subsequent health state corresponding to this event would be Health State 22 (step **2200**). If the patient is predicted to suffer from mild ischemic stroke **3014**, a subsequent health state corresponding to this event would be Health State 22 (step **2200**). If the patient is predicted to suffer from reversible ischemic stroke **3016**, a subsequent health state corresponding to this event would be Health State 25 (step **2500**).

[0262] The probability of the patient experiencing bleed events **3006** may be determined using the baseline risk profile generated by a bleed index, such as, for example, the ATRIA scores and probabilities, which may be adjusted by the increase in relative risk of recurrent bleeds and the relative risk for the selected treatment option as compared to warfarin. The relative risk of recurrent bleed may, for example, be at a rate of 1.5. If the patient is predicted to suffer from a bleed event **3006**, the patient may experience a fatal event **3018**, intra-cranial hemorrhage **3020**, major non-cranial hemorrhage, or minor hemorrhage **3024**. The probabilities of each of these bleed events may depend on the distribution of the severity of bleed events for the selected treatment option. If the patient is predicted to suffer from a fatal event **3018**, a subsequent health state corresponding to this event would be Health State 31, death **3100**. If the patient is predicted to suffer from intra-cranial hemorrhage **3020**, a subsequent health state corresponding to this event would be Health State 11 (step **1100**).

[0263] If the patient is predicted to suffer from a major non-cranial hemorrhage **3022**, the simulation may predict that the patient could be permanently discontinued from the existing course of treatment **3026**, which is the administration of the selected treatment option, and a subsequent health state corresponding to the bleed event and the new course of treatment would remain as Health State 25 (step **2500**). The patient may be permanently discontinued from the existing course of treatment **3026** at any rate. Preferably, the patient may be permanently discontinued from the existing course of treatment **3026** at a probability of 25%. Alternatively, the patient may remain under the selected treatment option **3028**, but may be temporarily discontinued from the existing course of treatment **3030** by a period of three months or 90 days. The patient may be temporarily discontinued from the existing course of treatment **3030** at any rate. Preferably, the patient may be temporarily discontinued from the existing course of treatment **3030** when the major non-cranial hemorrhage are gastrointestinal, which may, for example, be at a probability of 89.9%. If the patient is predicted to suffer from a major non-cranial hemorrhage **3022** and the simulation predicts that the patient is temporarily discontinued from the existing course of treatment **3030**, a subsequent health state corresponding to the bleed event and the new course of treatment would remain as Health State 25 (step **2500**). If the patient is predicted to suffer from a major non-cranial hemorrhage **3022** and the simulation predicts that the patient continues the existing course of treatment **3032**, a subsequent health state corresponding to the bleed event and the new course of treatment would remain as Health State 25 (step **2500**).

[0264] If the patient is predicted to suffer from a minor hemorrhage **3024**, a subsequent health state would be Health State 30 (step **3000**). Similarly, if the patient is predicted not to experience an adverse event **3008**, the simulation may predict that a subsequent health state would also remain as Health State 30 (step **3000**).

Health State 31 (step **3100**)

[0265] Health State 31 (step **3100**) represents when the patient is predicted to die from an adverse event, whether or not the adverse event is a stroke and/or bleed event.

EXAMPLE 7: APPLICATION OF MARKOV SIMULATION TO SAMPLE COHORT

[0266] A retrospective cohort analysis was conducted of persons diagnosed with atrial fibrillation in order to apply the risk benefit model discussed in Examples 1 and 3-6 above to a real-world sample cohort using two different approaches. Specifically, the data used is the MarketScan® Research Database, which is a proprietary U.S. database providing healthcare researchers access to fully integrated, de-identified, individual-level healthcare claims data from commercial insurers. Medstat MarketScan is a claims-level dataset capturing person-specific clinical utilization, expenditures, and enrollment across inpatient, outpatient, and prescription drug services. The data are drawn from roughly 45 large employers, health plans, and government organizations. Data from January 2003 through December 2007 were used in our analysis.

[0267] In one approach, the analysis employed a prevalence based methodology. The prevalence approach has the advantage of being composed of existing and newly diagnosed atrial fibrillation (AF) patients which provides a large and generalizable sample, but has the drawback that the temporal sequence of risks and events cannot be clearly elucidated. The second approach was to develop an incidence based cohort where only newly diagnosed atrial fibrillation patients were included. The incidence based approach is capable of more clearly describing the temporal sequence of risks prior to atrial fibrillation and would mirror the clinical situation of how newly diagnosed patients were treated, but would not be applicable to how all currently diagnosed patients are being treated. Both cohorts were entered into the decision analytic model to explore the impact the different cohort designs have on the modeled treatment recommendations.

[0268] The initial classification of the risk factors was defined as one or more primary or secondary diagnoses in the relevant time periods obtained from inpatient or medical claims. The study measures were derived by searching for any medical or inpatient claim with a primary or secondary diagnosis meeting the risk factors. For risk factors in the incidence cohort, only diagnoses occurring in the 12 month period prior to the incident (index) AF diagnosis were used to define risk factors. In the prevalence based cohort, the diagnoses occurring in the 12 month period after their first AF diagnosis was used. Study outcome measures were defined as those occurring in the incidence cohort in the 12 month period following the index AF diagnosis.

[0269] The stroke risk variables previously described in Example 1 were used to determine each patient's CHADS₂ score in the database. The stroke risk factors were

constructed as individual dummy variables and the CHADS₂ score was computed for each patient using the algorithm separately in the database as well as in the Markov model in order to provide a check that each patient was appropriately scored.

[0270] The ATRIA bleeding risk factors shown previously in Example 3 were used to calculate each patient's ATRIA score. Alternatively, the risk stratification scheme of Example 2 may also be used. Each patient was scored separately by the model and in the database.

[0271] For the prevalence based cohort, the number of prescriptions for each class of antithrombotic drug class was calculated. For the incidence based analysis, the count of each antithrombotic drug class was calculated in both the pre-index and post-index periods and ultimately grouped into no-exposure (zero prescriptions); partial exposure (1 to 292 days supply in year – 80% of days in year) and full exposure (>292 days supply). The drugs were mapped using GPI/GCN code classifications available in the Medstat Marketscan database. It is recognized that by using aspirin prescription claims, exposure to aspirin was underreported and will have to be recognized as a limitation.

[0272] 1. Warfarin (vitamin K antagonists)

[0273] 2. Aspirin and salicylates (TherClas 58)

[0274] 3. Clopidogrel, ticlopidine, dipyridamole, glycoprotein IIb/IIIa inhibitors (TherClass45)

[0275] New incident strokes, TIAs, Intracranial bleeds, and GI bleeds were defined as new events in the 12 month post-index time period for the incident cohort with a primary diagnosis. Persons were followed until they experienced an event or become censored (loss of eligibility or study end). Outcome measures, and include:

[0276] 1. Ischemic Stroke

[0277] 2. Transient Ischemic Attack (TIA)

[0278] 3. Intra Cranial Bleed

[0279] 4. Major non-cranial bleeds (GI)

[0280] 5. Other Bleeds

[0281] Demographic (age and gender) geographic locale (NorthEast, South, Midwest, West), index year, markers for use of gastro protective agents; antacids (TherClass=147), H2RAs (TherClass=161) PPIs and other GI protectants (TherClass=162), NSAIDs (TherClass=59), non topical glucocorticoid and mineralcorticosteroids (TherClass=166), immunosuppressants (therClass=181), heparin analogs (TherClass=39 – less warfarin), and chemotherapeutic agents (TherClass21) were also calculated in the pre and post-index periods.

[0282] To describe the stroke and bleeding risk variable for a cohort of subjects with AF based on the CHADS₂ and ATRIA indices, a data file was created for the incident and prevalence cohorts with a dummy variable for each stroke and bleed risk factor identified above. Additionally a CHADS₂ score and bleeding risk score were computed for each subject.

[0283] To determine the frequency warfarin would be recommended by the decision tool in a commercially insured population and contrast modeled oral anticoagulant treatment recommendations versus actual practice, cross tabulations (i.e. composite risk matrix) of the stroke index (CHADS₂ score) by the number of bleeding risk factors were developed and the cells were populated with frequency and percentages. Demarcations showing the cross tabulations where warfarin or aspirin was recommended by the model were made based on the modeling results. Ultimately the bleeding and stroke risks were categorized into three categories (low, moderate, and high) based on the thresholds described in Examples 1 and 3. Cross tabulations of the different risks were evaluated.

[0284] The shift in proportion of patients recommended for treatment in this population by reducing bleeding risk rates was explored by creating cross tabulations of the model-recommended warfarin prescribing versus that actual observed in the incidence and prevalence based cohorts. To provide a treatment recommendation for the patients in the cohort, a second order Monte Carlo Simulation analysis was conducted, sampling each row of patient data in both the incidence and prevalence cohort. For each patient or sample, the simulation analysis was performed using expected value calculations to determine the QALYs for each treatment strategy. The strategy with the greatest QALY was considered the

“Recommended” approach. The output for each patient’s modeled results was re-merged with the original data.

[0285] To explore factors that are related to over prescribing or under prescribing of warfarin, univariate comparisons were made across demographic (age, gender) and comorbidity categories contrasting when warfarin was used or not used; Chi square tests were used to test for univariate differences.

[0286] The results of the model’s recommendation using the 64-patient default cohort from Example 4 are shown below in Table 22.

Table 22.

Sample	QALY Warf.	QALY Asp.	Sample (cont.)	QALY Warf (cont.)	QALY Asp. (cont.)
1	7.810473937	7.799562593	33	6.65320204	6.657572629
2	7.766585518	7.782139223	34	6.365626749	6.383732892
3	7.743581718	7.773868222	35	6.324287379	6.353037739
4	7.651140578	7.701643094	36	6.221732283	6.275717259
5	7.653258452	7.703283334	37	6.221732283	6.275717259
6	7.526432247	7.605121508	38	6.221732283	6.275717259
7	7.567766688	7.531278236	39	4.626872554	3.674231963
8	7.550542552	7.526071217	40	4.619638006	3.67268331
9	7.51167568	7.512721617	41	4.426402866	3.559207506
10	7.480893637	7.503460267	42	4.589009997	3.665976772
11	7.389293814	7.432646499	43	4.311464235	3.536270015
12	7.391378739	7.43424573	44	4.313681586	3.536707949
13	7.314313863	7.375521038	45	4.235072007	3.520822554
14	7.267370657	7.339067232	46	4.189334314	3.510268094
15	7.149065533	7.246201172	47	4.083475636	3.486169463
16	6.890966998	6.980252523	48	4.083475636	3.486169463
17	7.27725714	7.207032625	49	4.083475636	3.486169463
18	7.255734628	7.201486542	50	4.144790818	3.100251681
19	7.207426501	7.187298234	51	3.987103656	3.01861455
20	7.168660819	7.176136588	52	3.977235033	3.015371896
21	7.076725095	7.107771108	53	3.880258622	2.999763573
22	7.078781623	7.109326082	54	3.882306681	3.000111394
23	7.003134623	7.051624804	55	3.809531204	2.987554611
24	6.95742067	7.016581465	56	3.767087392	2.979091374
25	6.843082777	6.927813451	57	3.668741565	2.960330643
26	6.609009392	6.68661005	58	3.668741565	2.960330643
27	6.609009392	6.68661005	59	3.668741565	2.960330643
28	5.001093029	4.186412483	60	3.487338045	2.487716471
29	6.85259634	6.749444385	61	3.406562374	2.475198129
30	6.564549976	6.5047685	62	3.306776996	2.460038269
31	6.741754231	6.722166118	63	3.22097148	2.446036899
32	6.432757915	6.433317735	64	3.22097148	2.446036899

[0287] The individual QALY's for warfarin and aspirin are provided in Table 22. As shown in Figure 35, the mean QALYs for warfarin over the cohort exceeded aspirin at 5.77 versus 5.44. Treatment is optimized across the composite risk matrix cohort 56% of the time with warfarin and 43% of the time with aspirin.

[0288] Table 23 and Table 24 below provide the model's recommendation for each cell of the risk matrix both in detailed form as well as grouped by overall risk category for a

patient cohort 74-75 years old. For the default 74-75 year old patient cohort the model recommendations appear generally consistent with our interpretation of the treatment guidelines. Warfarin is recommended for all of the high stroke risk patients, aspirin is recommended for most of the low stroke risk patients, and warfarin is recommended selectively for moderate stroke risk patients depending on their bleeding risk. It is notable, however, that for the low stroke, low bleed risk patient our model recommends Warfarin. For high-moderate patients, aspirin is recommended for an ATRIA score of 4 and up; for low-moderates this threshold is at an ATRIA above 2.

Table 23.

CHADS ₂ Score	High	6	NA	NA	NA	W	NA	W	NA	W	W	NA	W
		5	NA	W	W	W	W	W	W	W	W	W	W
		4	W	W	W	W	W	W	W	W	W	W	W
	Mod.	3	W	W	W	W	A	A	A	A	A	A	A
		2	W	W	W	A	A	A	A	A	A	A	A
	Low	1	W	W	A	A	A	A	A	A	A	A	NA
		0	W	NA	A	A	A	A	NA	A	NA	NA	NA
W = Warfarin A = Aspirin		0	1	2	3	4	5	6	7	8	9	10	
		Low		Moderate		High							
		ATRIA Score											

Table 24.

CHADS ₂ Score	High	Warfarin	Warfarin	Warfarin
	Mod.	Warfarin	Warfarin	Aspirin
	Low	Warfarin	Aspirin	Aspirin
		Low	Moderate	High
		ATRIA Score		

[0289] Table 25 below provide the model's recommendation for each cell of the risk matrix both in detailed form as well as grouped by overall risk category for a patient cohort 61 years old.

Table 25.

CHADS ₂ Score	High	6	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
		5	NA	W	NA	W	W	W	W	NA	W	NA	NA
		4	W	W	W	W	W	W	W	W	W	NA	NA
	Mod.	3	W	W	W	A	A	A	A	A	A	NA	NA
		2	W	W	A	A	A	A	A	A	A	NA	NA
	Low	1	W	A	A	A	A	A	A	A	A	NA	NA
		0	A	NA	A	A	A	A	NA	A	NA	NA	NA
W = Warfarin A = Aspirin		0	1	2	3	4	5	6	7	8	9	10	
		Low		Moderate		High							
		ATRIA Score											

[0290] Table 26 below provide the model's recommendation for each cell of the risk matrix both in detailed form as well as grouped by overall risk category for a patient cohort 82 years old.

Table 26.

CHADS ₂ Score	High	6	NA	NA	NA	W	NA	W	NA	W	W	NA	W
		5	NA	NA	W	W	W	W	W	W	W	W	W
		4	NA	NA	W	W	W	W	W	W	W	W	W
	Mod.	3	NA	NA	W	W	W	W	W	A	A	A	A
		2	NA	NA	W	W	A	A	A	A	A	A	A
	Low	1	NA	NA	W	NA	A	A	A	A	NA	A	NA
		0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
W = Warfarin A = Aspirin		0	1	2	3	4	5	6	7	8	9	10	
		Low		Moderate		High							
		ATRIA Score											

EXAMPLE 8: DATA ANALYSIS AND MODEL RESULTS FOR MARKETSCAN COHORT

[0291] A sample cohort derived from the MarketScan® Research Database, after applying inclusion and exclusion criteria was formed with a sample of incident and prevalent AFIB patients of 64,946 and 239,660 respectively.

[0292] Table 27 below shows that for the incident cohort, the majority of patients in the Marketscan sample fall into the low stroke, low bleed risk category; followed by the moderate stroke, moderate bleed risk category.

Table 27.

Population Distribution CHADS₂ by ATRIA (Incidence Cohort)				
CHADS₂	ATRIA SCORE			
Frequency Percent Row Pct Col Pct				
	0-1: Low	2-3: Medium	4+: High	Total
0-1: Low	25,562	11,155	2029	38,746
	3936	17.18	3.12	59.66
	65.97	28.79	5.24	
	8533	40.85	26.42	
2-3: Medium	4,102	13,895	4,406	22,403
	632	21.39	6.78	34.49
	1831	62.02	19.67	
	13.69	50.88	57.38	
4+: High	294	2259	1,244	3,797
	0.45	3.48	1.92	5.85
	7.74	59.49	32.76	
	0.98	8.27	162	
Total	29,958	27,309	7,679	64,946
	46.13	42.05	11.82	100

[0293] This observation holds true for the prevalence cohort as well (Table 28 below). Due to overlapping covariates between CHADS₂ and ATRIA there are few (but some) patients that are have both a high stroke and low bleed risk (<1%). Conversely the high bleed and low stroke risk category does have more patients, but still makes up less than 4% of the total population.

Table 28.

Population Distribution CHADS₂ by ATRIA (Prevalence Cohort)				
CHADS₂	ATRIA SCORE			
Frequency				
Percent				
Row Pct				
Col Pct	0-1: Low	2-3: Medium	4+: High	Total
0-1: Low	72,516 30.26 61.66 76.29	35,977 15.01 30.59 35.53	9,110 3.8 7.75 21.01	117,603 49.07
2-3: Medium	20,741 8.65 20.64 21.82	54,482 22.73 54.21 53.81	25,283 10.55 25.16 58.31	100,506 41.94
4+: High	1,798 0.75 8.34 1.89	10,786 4.5 50.05 10.65	8,967 3.74 41.61 20.68	21,551 8.99
Total	95,055 39.66	101,245 42.25	43,360 18.09	239,660 100

[0294] Table 29 below shows the model recommendations after processing each patient in the incidence cohort.

Table 29.

Stroke Risk vs. Bleeding Risk vs. Model Recommendation. Incidence Cohort, Default Rates									
Model			Aspirin	Warfarin	Aspirin	Warfarin	Aspirin	Warfarin	
Stroke Risk (CHAD ₂)	High		0	294	0	2,259	40	1,204	3,797
	Mod.		54	4,048	2,439	11,456	3,102	1,304	22,403
	Low		16,056	9,506	3,446	7,709	2,029	0	38,746
	All		16,110	13,848	5,885	21,424	5,171	2,508	64,946
			Low		Moderate		High		All
			Bleeding Risk (ATRIA)						

[0295] The recommendation is straight forward across the high stroke risk categories, with nearly 100% of patients recommended for warfarin. The variability of treatment recommendations in the low stroke, moderate bleed segment is noteworthy when the model is applied to large these samples. In contrast, the default 74-75 year old cohort only provides a single recommendation per cell, because it represents only one patient. This underscores the need to evaluate each patient for a treatment recommendation regardless of their position in the matrix. For example, a greater percentage of the low stroke, moderate bleed category was recommended for warfarin (in contrast to the default age 74-75 cohort). However, 100% of the patients in this category who are recommended for warfarin have a CHADS₂ score of 1 (high end of low stroke) and an ATRIA score of 2 (low end of moderate bleed). Furthermore, in this group the warfarin recommended patients are all 75 years of age or older with a mean age of 82, versus the aspirin recommended patients who are younger, having a mean age of

75. As show in Table 21, using the 82 year old cohort, our model recommends warfarin for low stroke, moderate bleed risk patients.

[0296] Table 30 shows the number of patients for whom the model recommends aspirin or warfarin and their respective actual exposure to warfarin.

Table 30.

Actual Warfarin Exposure vs. Model Recommendation: Incidence Cohort, Default Model Rates																					
Model		Aspirin			Warfarin			Aspirin			Warfarin			Aspirin			Warfarin			All	
Actual Warfarin Exposure		Full	Partial	No	Full	Partial	No	Full	Partial	No	Full	Partial	No	Full	Partial	No	Full	Partial	No		
Stroke Risk (CHADS ₂)	High	0				123	131	0	0	0	279	922	1,058	4	17	19	98	439	667	3,797	
	Mod.	2	19	33	663	1,832	1,553	372	1,190	877	1,494	4,628	5,334	298	1,218	1,586	108	448	748	22,403	
	Low	1,548	5,573	8,935	1,699	4,365	3,442	439	1,384	1,623	947	3,137	3,625	199	767	1,063	0	0	0	38,746	
	ALL	1,550	5,592	8,968	2,402	6,320	5,126	811	2,574	2,500	2,720	8,687	10,017	501	2,002	2,668	206	887	1,415	64,946	
		Low					Moderate					High					All				
		Bleeding Risk (ATRIA)																			

[0297] In Table 31 the actual warfarin exposure breakdown are shown for patients that were recommended for warfarin only by the model.

Table 31.

		Model Rcmndtn (Warfarin)	% Actual Warfarin Exposure (Any)	% Actual Warfarin Exposure (Full)	Model Rcmndtn (Warfarin)	% Actual Warfarin Exposure (Any)	% Actual Warfarin Exposure (Full)	Model Rcmndtn (Warfarin)	% Actual Warfarin Exposure (Any)	% Actual Warfarin Exposure (Full)
Stroke Risk (CHADS ₂)	High	294	55.44%	13.61%	2,259	53.17%	12.35%	1,204	44.60%	8.14%
	Mod.	4,048	61.64%	16.38%	11,456	53.44%	13.04%	1,304	42.64%	8.28%
	Low	9,506	63.79%	17.87%	7,709	52.98%	12.28%	0	.	.
		Low			Moderate			High		
		Bleeding Risk (ATRIA)								

[0298] Similarly, Table 32 shows the percentage of patients that had no exposure to warfarin for whom the model recommends aspirin only.

Table 32

Percentage NO Warfarin Exposure vs. Aspirin Recommended: Incidence							
		Model Rcmdtn (Aspirin)	% Warfarin Exposure (NO)	Model Rcmdtn (Aspirin)	% Warfarin Exposure (NO)	Model Rcmdtn (Aspirin)	% Warfarin Exposure (NO)
Stroke Risk (CHADS ₂)	High	0	.	0	.	40	47.50%
	Mod.	54	61.11%	2,439	35.96%	3,102	51.13%
	Low	16,056	55.65%	3,446	47.10%	2,029	52.39%
		Low		Moderate		High	
		Bleeding Risk (ATRIA)					

[0299] Table 33 below shows the model recommendations after processing each patient in the prevalence cohort.

Table 33.

Stroke Risk vs. Bleeding Risk vs. Model Recommendation: Prevalence Cohort, Default Rates								
Model		Aspirin	Warfarin	Aspirin	Warfarin	Aspirin	Warfarin	
Stroke Risk (CHADS ₂)	High	0	1,798	7	10,779	507	8,460	21,551
	Mod	229	20,512	9,808	44,674	17,724	7,559	100,506
	Low	39,706	32,810	13,448	22,529	9,110	0	117,603
	ALL	39,935	55,120	23,263	77,982	27,341	16,019	239,660
		Low		Moderate		High		All
		Bleeding Risk (ATRIA)						

[0300] Table 34 shows the number of patients for whom the model recommends aspirin or warfarin and their respective actual exposure to warfarin.

Table 34.

Model Recommendation:		Aspirin			Warfarin			Aspirin			Warfarin			Aspirin			Warfarin			ALL	
Actual Warfarin Exposure		Full	Partial	No	Full	Partial	No	Full	Partial	No	Full	Partial	No	Full	Partial	No	Full	Partial	No		
Stroke Risk (CHADS 2)c/	High	0	0	0	369	940	489	0	4	3	1,897	5,383	3,499	52	278	177	1,071	4,422	2,967	21,551	
	Mod	19	70	140	4,220	9,716	6,576	1,835	4,692	3,281	8,810	20,195	15,669	2,617	8,808	6,299	1,096	3,653	2,810	100,506	
	Low	5,059	13,088	21,559	7,040	14,817	10,953	2,350	6,054	5,044	4,420	9,695	8,414	1,427	4,248	3,435	0	0	0	117,603	
	ALL	5,078	13,158	21,699	11,629	25,473	18,018	4,185	10,750	8,328	15,127	35,273	27,582	4,096	13,334	9,911	2,167	8,075	5,777	239,660	
		Low						Moderate						High						All	
		Bleeding Risk (ATRIA)																			

[0301] In Table 35 the actual warfarin exposure breakdown are shown for patients that were recommended for warfarin only by the model.

Table 35.

Percentage Actual Warfarin Exposure vs. Model Recommendation. Prevalence Cohort, Default Model Rates										
		Model Remndtn (Warfarin)	% Actual Warfarin Exposure (Any)	% Actual Warfarin Exposure (Full)	Model Remndtn (Warfarin)	% Actual Warfarin Exposure (Any)	% Actual Warfarin Exposure (Full)	Model Remndtn (Warfarin)	% Actual Warfarin Exposure (Any)	% Actual Warfarin Exposure (Full)
Stroke Risk (Chads ₂)	High	1,798	72.80%	20.52%	10,779	67.54%	17.60%	8,460	64.93%	12.66%
	Mod.	20,512	67.94%	20.57%	44,674	64.93%	19.72%	7,559	62.83%	14.50%
	Low	32,810	66.62%	21.46%	22,529	62.65%	19.62%	0	.	.
		Low			Moderate			High		
Bleeding Risk (ATRIA)										

[0302] Similarly, Table 36 shows the percentage of patients that had no exposure to warfarin for whom the model recommends aspirin only.

Table 36.

		Model Remndtn (Aspirin)	% Warfarin Exposure (NO)	Model Remndtn (Aspirin)	% Warfarin Exposure (NO)	Model Remndtn (Aspirin)	% Warfarin Exposure (NO)
Stroke Risk (CHADS ₂)	High	0	.	7	42.86%	507	34.91%
	Mod.	229	61.14%	9,808	33.45%	17,724	35.54%
	Low	39,706	54.30%	13,448	37.51%	9,110	37.71%
		Low		Moderate		High	
		Bleeding Risk (ATRIA)					

EXAMPLE 11: SENSITIVITY ANALYSIS

[0303] Using the ATRIA cohort, Singer et al., “The Net Clinical Benefit of Warfarin Anticoagulation in Atrial Fibrillation,” Ann Intern Med. 151: 297-305 (2009) observed substantially lower than previously published stroke rates for patients taking warfarin. These rates are approximately 50% lower than the default rates in the model taken from Gage, et al., “Validation of Clinical Classification Schemes for Predicting Stroke: Results From the National Registry of Atrial Fibrillation,” JAMA, Vol. 285, No. 22, 2864-2870 (2001).

[0304] To evaluate the impact that these lower stroke rates have on our model’s treatment recommendation, a sensitivity analysis utilizing lower rates CHADS₂ score as shown in Table 37 below.

Table 37.

CHADS ₂ Score	Stroke Rate (per 100 patient years)	Risk Category
0	0.37	Low
1	1.19	
2	2.54	Moderate
3	3.89	
4	6.34	High
5	6.34	
6	6.34	

[0305] By substituting these lower stroke rates in the model, it can be seen that a greater number of risk cells where aspirin is the recommended treatment (Table 38), with two cells changing from warfarin to aspirin, where CHADS₂ score is 0 and ATRIA score is 0 and where CHADS₂ score is 1 and ATRIA score is 1.

Table 38.

CHADS ₂ Score	High	6	NA	NA	NA	W	NA	W	NA	W	W	NA	W
		5	NA	W	W	W	W	W	W	W	W	W	W
		4	W	W	W	W	W	W	W	W	W	W	W
	Mod.	3	W	W	W	W	A	A	A	A	A	A	A
		2	W	W	W	A	A	A	A	A	A	A	A
	Low	1	W	A	A	A	A	A	A	A	A	A	NA
		0	A	NA	A	A	A	A	NA	A	NA	NA	NA
W = Warfarin A = Aspirin		0	1	2	3	4	5	6	7	8	9	10	
		Low		Moderate		High							
		ATRIA Score											

[0306] From the standpoint of overall risk categories (Table 39), one risk category (Low Stoke, Low Bleed Risk) changes from warfarin to aspirin recommended.

Table 39.

CHADS ₂ Score	High	Warfarin	Warfarin	Warfarin
	Mod.	Warfarin	Warfarin	Aspirin
	Low	Aspirin	Aspirin	Aspirin
		Low	Moderate	High
		ATRIA Score		

EXAMPLE 12: IMPACT OF BLEED RISK REDUCTION ON WARFARIN

[0307] In order to evaluate the potential impact that newer anticoagulants would have on treatment recommendations if they were to offer a superior bleed risk profile, a sensitivity analysis may be conducted by uniformly reducing the bleeding risk across each ATRIA score. Simulations maybe performed using 10% and 30% bleed reduction for warfarin. No other model parameters were changed, such as adherence rates. This has the benefit of isolating the impact of changing bleed rates, but the drawback of not considering the possible improvements in drug adherence with improved bleed risk profile. The results are shown in below in Table 40 and Table 41 use the default 64-patient cohort of Example 4 with a 10% warfarin bleed rate reduction. Versus the baseline matrix, warfarin is recommended in four additional risk cells at a 10% bleeding risk reduction, but this has no impact at the category level.

Table 40.

CHADS ₂ Score	High	6	NA	NA	NA	W	NA	W	NA	W	W	NA	W
		5	NA	W	W	W	W	W	W	W	W	W	W
		4	W	W	W	W	W	W	W	W	W	W	W
	Mod.	3	W	W	W	W	W	W	A	A	A	A	A
		2	W	W	W	W	A	A	A	A	A	A	A
	Low	1	W	W	W	A	A	A	A	A	A	A	NA
		0	W	NA	A	A	A	A	NA	A	NA	NA	NA
W = Warfarin A = Aspirin		0	1	2	3	4	5	6	7	8	9	10	
		Low		Moderate		High							
		ATRIA Score											

Table 41.

CHADS ₂ Score	High	Warfarin	Warfarin	Warfarin
	Mod.	Warfarin	Warfarin	Aspirin
	Low	Warfarin	Aspirin	Aspirin
		Low	Moderate	High
		ATRIA Score		

[0308] The results are shown in below in Table 42 and Table 43 use the default 64-patient cohort of Example 4 with a 30% warfarin bleed rate reduction. With a 30% bleed risk reduction, warfarin is recommended in an additional seven risk cells, also with no impact at the category level.

Table 42.

CHADS ₂ Score	High	6	NA	NA	NA	W	NA	W	NA	W	W	NA	W
		5	NA	W	W	W	W	W	W	W	W	W	W
		4	W	W	W	W	W	W	W	W	W	W	W
	Mod.	3	W	W	W	W	W	W	W	W	A	A	A
		2	W	W	W	W	A	W	A	A	A	A	A
	Low	1	W	W	W	A	A	A	A	A	A	A	NA
		0	W	NA	A	A	A	A	NA	A	NA	NA	NA
W = Warfarin A = Aspirin		0	1	2	3	4	5	6	7	8	9	10	
		Low		Moderate		High							
		ATRIA Score											

Table 43.

CHADS ₂ Score	High	Warfarin	Warfarin	Warfarin
	Mod.	Warfarin	Warfarin	Aspirin
	Low	Warfarin	Aspirin	Aspirin
		Low	Moderate	High
		ATRIA Score		

[0309] Table 44 provides the results from each of the sensitivity analysis variations in the incidence cohort to identify the shift in number of patients recommended for warfarin verses aspirin within each risk category. As shown below, a 10% bleed reduction with warfarin leads to an additional 5,309 warfarin recommendations. While lowering the stroke risk leads to 20,213 more aspirin recommendations, lowering the bleed risk by 30% and the stroke rate simultaneously leads to an additional 12,621 aspirin recommendation, versus the base case rates.

Table 44.

	Basecase	10% Warfarin Bleed Reduction	30% Warfarin Bleed Reduction	Lower Stroke Rates	30% Bleed Reduction & Lower Stroke Rates
Patients Recommended Warfarin	37,780	43,089	51,567	17,567	25,159
Patients Recommended Aspirin	27,166	21,857	13,379	47,379	39,787
Additional Patients Recommended Aspirin vs. Basecase	---	(5,309)	(13,787)	20,213	12,621

EXAMPLE 13: APPLICATION OF MARKOV SIMULATION TO SAMPLE COHORT

[00310] A retrospective cohort analysis was also conducted of using an exemplary patient cohort derived from 64,946 patients newly diagnosed with nonvalvular atrial fibrillation (NVAF) identified from the MarketScan® database. Medicare patients are included in the MarketScan sample if they have some form of other commercial insurance or have commercially managed Medicare. Patients in this cohort were ≥ 18 years of age, had at least two medical claims with atrial fibrillation (AF) (ICD-9-CM code 427.31) as primary diagnosis (one of the AF claims was required to be an outpatient claim and at least one set of AF claims must have been separated by ≥ 30 days), were continuously eligible for ≥ 12 months prior to the index (first) AF medical claim, and had no AF medical claim in the 12 month pre-index period. Patients were excluded if they had any medical claim suggesting the presence of valvular and/or transient AF, such as mitral stenosis, valvular repair or replacement, or transient post-operative AF, had prior warfarin use, or died at the time of their index AF diagnosis. The demographic characteristics of the sample cohort used are summarized below in Table 45. The mean age for this sample cohort of patients was 70.9 years and the most common comorbidities were hypertension (46.4%), diabetes (17.9%), and heart failure (11.3%).

Table 45.

Exemplary patient cohort from Marketscan® database	
Total number of subjects, N	64,946
Mean age, yrs (standard deviation)	70.91 (13.47)
<i>Age Category, y</i>	<i>n (%)</i>
18–30	323 (0.5%)
31–49	4250 (6.54%)
50–64	16,480 (25.37%)
65–74	13,483 (20.76%)
75–84	20,929 (32.23%)
≥85	9481 (14.60%)
<i>Gender</i>	<i>n (%)</i>
Female	29,141 (44.87%)
<i>Geographic Region</i>	<i>n (%)</i>
Northeast	5957 (9.17%)
North Central	22,753 (35.03%)
South	20,808 (32.04%)
West	15,152 (23.33%)
Unknown	276 (0.42%)
<i>Comorbidities</i>	<i>n (%)</i>
Prior stroke or transient ischemic attack.	5004 (7.70%)
Hypertension	30,147 (46.42%)
Diabetes	11,604 (17.87%)
Heart failure	7312 (11.26%)
Anemia	5091 (7.84%)
History of any bleed	5711 (8.79%)
Renal impairment	2378 (3.66%)

[0311] The stroke risk variables previously described in Example 1 were used to determine each patient's CHADS₂ score. The stroke risk factors were constructed as individual dummy variables and the CHADS₂ score was computed for each patient using the algorithm separately in the database as well as in the Markov model in order to provide a check that each patient was appropriately scored.

[0312] The ATRIA bleeding risk factors shown previously in Example 2 were used to calculate each patient's ATRIA score. Alternatively, the risk stratification scheme of Example 3 may also be used. Each patient was scored separately.

[00313] Patients with a CHADS₂ score of 0 or 1, 2 or 3, and 4 to 6 were considered to have low, moderate, and high stroke risk, respectively; and ATRIA bleeding risk index scores were summarized as low (score = 0–3), moderate (score = 4), and high (score = 5–10). The proportions of patients recommended to receive warfarin or aspirin by the model were summarized at each level of stroke and bleeding risk score and then summarized by low, moderate, or high scores of their respective risk assessment tool. The proportion of patients who received at least one warfarin prescription after index AF diagnosis, were then compared with model recommendations at each stroke and bleeding risk level. The distributions of risk for stroke according to the CHADS₂ scores (Example 1) and bleeding according to the ATRIA scores of Example 3 are summarized below in Table 46 and Table 47 (the percentages shown therein represents % per CHADS₂ risk category of low, moderate, or high).

Table 46

CHADS ₂ Score	High	6				81	16		35	17		20	12
		5		46	56	431	85	18	122	67	12	33	16
		4	26	224	313	1381	238	59	291	94	13	67	24
	Mod.	3	130	756	937	2578	389	165	528	198	46	121	43
		2	528	2755	2596	7813	1048	412	886	295	45	95	39
	Low	1	2414	8275	9486	755	468	701	135	52	55	7	
		0	15065	819		394	89		27	4			
			0	1	2	3	4	5	6	7	8	9	10
		Low				Mod.	High						
		ATRIA Score											

Table 47.

ATRIA Score	High	981 (2.5%)	2873 (12.8%)	900 (23.7%)
	Mod.	557 (1.4%)	1437 (6.4%)	339 (8.9%)

	Low	37,208 (96%)	18,093 (80.7%)	2558 (67.4%)
		Low	Moderate	High
		CHADS ₂ Score		

[0314] Of the 64,946 patients entered in the simulation, 40.3% (n = 26,200) had CHADS₂ scores ≥ 2 and an additional 34.4% (n = 22,348) had a CHADS₂ score of 1. Assessment of ATRIA bleed risk scores indicated that 10.9% (n = 7,087) of patients had moderate/high bleeding risk (ATRIA scores ≥ 4). As stroke risk increased, the percent of patients with moderate/high bleeding risk also rose. Among patients with low stroke risk (CHADS₂ score of 0 or 1), only 3.9% (n = 1,488) had moderate/high risk for bleeding (ATRIA score ≥ 4). Overall, 32.6% (n = 1,239) of subjects with CHADS₂ scores ≥ 4 had moderate/high bleeding risk.

[0315] To determine the frequency warfarin would be recommended by the simulation in a commercially insured population and contrast simulated oral anticoagulant treatment recommendations versus actual practice, using the a risk benefit model similar to those discussed in Examples 4-6 above. Patients from the exemplary cohort enter the simulation model in a well state with atrial fibrillation and transitioned along decision pathways to one of the following mutually exclusive health states: well state with AF, transient ischemic attack (TIA), stroke without permanent disability, mild stroke or moderate/severe stroke with permanent morbidity, intracranial hemorrhage, extracranial major hemorrhage, minor hemorrhage, or death. The simulation iterated every 90 days. The probability of transitioning from one health state to another during a cycle was determined based on a patient's baseline stroke and bleeding risk profiles, prior health states, stroke prevention treatment, and age and gender-specific life expectancy. The simulation was terminated when >99.9% of the simulated cohort died. All health outcomes were discounted at an annual rate of 3%.

[0316] In this embodiment, patients who experienced an ICH were assumed to discontinue warfarin treatment permanently. For patients who experienced a non-fatal major extracranial hemorrhage, 25% of patients were assumed to discontinue warfarin permanently,

and 66.7% patients discontinued warfarin treatment for 3 months and resumed treatment. For patients who did not experience any adverse events, a discontinuation rate of 26.5% was assumed during the first year of warfarin treatment, followed by a 6.5% discontinuation rate in the second year, and stabilized to an annual discontinuation rate of 1.2% after 4 years of treatment. In addition, aspirin discontinuation rate was estimated by applying the risk ratio of aspirin versus warfarin discontinuation from the Birmingham Atrial Fibrillation Treatment of the Aged Study (BAFTA), as described in Mant et al., “Warfarin versus aspirin for stroke prevention in an elderly community population with atrial fibrillation (the Birmingham Atrial Fibrillation Treatment of the Aged Study, BAFTA), Lancet, 370: 493-503 (2007) to warfarin discontinuation rates, as described in Fang et al., “Warfarin discontinuation after starting warfarin for atrial fibrillation, “ Circ. Cardiovasc. Qual. Outcomes, 3:624-631 (2010). Patients who discontinued warfarin treatment were assumed to experience stroke and bleeding events at the same rate as patients not receiving warfarin treatment. It is contemplated that these rates for discontinuing warfarin treatment may be utilized in any simulation where warfarin is a treatment option.

[0317] For the each period of life predicted by the simulation, an amount of quality adjusted life years (QALY) may be accrued. For example, a patient having a full year of life predicted by the simulation with full-health, the patient may accrue a QALY of 1. Death may be represented by a QALY of 0. For example, for each iteration that occurs every 3 months or 90 days, a QALY of 0 to approximately 0.25 may be accrued. Patients predicted to suffer from permanent disabilities would remain at a diminished state of health ($QALY < 1$) for the remaining duration of their life predicted by the simulation. Patients predicted to suffer from temporary disabilities may return to their baseline health status after leaving a non-permanent disability state. In particular, patients that are well and on warfarin may accrue a slightly lower QALY than those on aspirin for each period of predicted life in view of the compliance burden for warfarin administration on the patient. In this example, the QALY benefits of each treatment may be estimated using the following exemplary value reduction for reductions in the patient's quality of life or life style under the selected shown in Table 48. It is contemplated that these rates for discounting QALY benefits may be utilized in whole or in part for any of conditions or treatment options listed in Table 48.

Table 48.

Quality-of-Life Impairment (Disutility) Parameters	QALY Reduction
Initiation of warfarin treatment	-0.02
Stabilized on warfarin treatment	-0.013
Receiving aspirin treatment	-0.002
Transient ischemic attack (reversible stroke)	-0.2
Mild ischemic stroke	-0.25
Moderate/severe ischemic stroke or ICH	-0.61
Recurrent stroke	-0.88
Major ECH	-0.2
Minor bleed	-0.0010959

[0318] Aside from mortality due to stroke or hemorrhagic events during the course of treatment, the simulation also accounts for natural life expectancy for each subject in the simulated cohort not directly linked to these adverse events. The model terminated when all patients had died. Age and gender-specific mortality rates were applied from U.S. Vital Statistics Data to govern the probability of death for atrial fibrillation patients in the absence of adverse events and for patients who survived a prior stroke or ICH.

[0319] The simulation estimated an average life expectancy of 11.3 years and a quality-adjusted life expectancy of 8.4 years. Overall, the simulation recommended warfarin for 44,611 patients (68.7%). The mean quality-adjusted survival difference between the aspirin and warfarin was 1.8 months, with 56.7% having a quality-adjusted survival difference of 30 or more days between the two strategies. The results of the simulations' recommendations are compared to actual therapy are shown below in Table 49. The column labeled "Recomm. by Simulation" reflects treatment options recommended by the simulation and the column labeled "Actual use" reflects actual administration of warfarin at any time following atrial fibrillation diagnosis.

Table 49.

		Warfarin Utilization								
		Total # in risk category	Recomm. by Simulation	Actual Use	Total # in risk category	Recomm. by Simulation	Actual Use	Total # in risk category	Recomm. by Simulation	Actual Use
CHADS ₂	High Stroke Risk (≥4)	2558	100% (n=2558)	58.7% (n=1501)	339	100% (n=339)	51.9% (n=176)	900	97.1% (n=874)	50.8% (n=444)

	Moderate Stroke Risk (2-3)	18,093	99.7% (n=18,043)	64.1% (n=11,574)	1437	76.7% (n=1102)	59.0% (n=650)	2873	46.3% (n=1330)	48.1% (n=640)
	Low Stroke Risk (1)	20,930	97.3% (n=20,365)	65.3% (n=13,304)	468	0%	0%	950	0%	0%
		Low Bleeding Risk (0-3)			Moderate Bleeding Risk (4)			High Bleeding Risk (≥5)		
		ATRIA Score								

[0320] In general, the frequencies of stroke and bleed risk parallel one another, and both are skewed toward low to moderate risk groups of patients. Thus, patients at high risk for both stroke and bleeding comprise relatively small numbers of the dataset. All patients with $\text{CHADS}_2 = 0$ are recommended for aspirin by the simulation. As shown in Table 49, almost all patients with CHADS_2 scores ≥ 4 are recommended for warfarin. Thus, if a patient is not a warfarin candidate, the simulations recommends aspirin. Warfarin is recommended for almost all patients (97.3%) with CHADS_2 scores of 1 where ATRIA scores are < 4 , and aspirin was recommended 100% of the time when bleeding risk was either moderate or high (ATRIA score ≥ 4). Nearly all patients (99.3%) at high risk for stroke ($\text{CHADS}_2 \geq 4$) were recommended for warfarin regardless of bleeding risk. While 91.4% of patients with CHADS_2 scores of 2–3 may benefit from warfarin, the majority (53.7%) of those who also have a high bleeding risk (ATRIA score ≥ 5) had higher simulated quality-adjusted life expectancy (QALY) with aspirin.

[0321] The results of Table 49 also indicate that actual warfarin prescribing (at least one warfarin prescription after the index diagnosis of atrial fibrillation) was substantially lower than recommended by the simulation across all categories of stroke and bleeding risk. Most notably, while patients at high risk for stroke were recommended to receive warfarin in 100% of cases where bleeding risk is low or moderate and in 97.1% of cases where bleeding risk is high, actual warfarin prescribing ranged from 58.7% for patients at low bleeding risk to 50.8% for those at high risk. It was observed that actual warfarin prescribing had little relation to CHADS_2 stroke risk or ATRIA bleed risk. Rather, there was a relatively uniform level of anticoagulation despite guidelines recommending warfarin in patients with at least two risk factors for stroke who are not at high risk for bleeding.

[0322] As can be seen from the data shown in Table 49, anticoagulation is under-prescribed in patients with atrial fibrillation. By incorporating both the CHADS₂ and the ATRIA schemes, the simulation described in this Example integrates two risk assessment tools and provides data that have the potential to improve outcomes in patients with atrial fibrillation by improving the risk-benefit analysis. These findings underscore the unmet need for a better way to identify AF patients who can benefit from anticoagulation treatment. Results from this exemplary simulation as shown in Table 49 indicates that warfarin is recommended for almost all patients with CHADS₂ scores of 1 where ATRIA scores are < 4. For patients with low stroke risk, aspirin is recommended 100% of the time when bleeding risk is either moderate or high (ATRIA score $\geq$ 4). Generally all high stroke risk patients were recommended warfarin regardless of bleeding risk (99.3%). While 91.4% of patients with CHADS₂ scores of 2–3 may benefit from warfarin, the majority (53.7%) of those who also have a high bleeding risk (ATRIA score $\geq$ 5) may benefit from aspirin.

EXAMPLE 14: SENSITIVITY ANALYSIS

[0323] Because the base case analysis involved a number of assumptions, univariate sensitivity analyses were conducted to evaluate the effect of changes in key variables on the treatment recommendations provided by the exemplary simulation described in Example 13 above. The sensitivity analysis was conducted using scenarios where baseline stroke rates by CHADS₂, baseline major bleeding rates by ATRIA index, and the relative risk for stroke and bleeding for warfarin versus aspirin were increased and decreased by 10%. Table 50 provides data from the sensitivity analysis of the simulation described above in Example 13.

Table 15.

Changes to Base Case	Change in % of Patient Recommended Warfarin by Exemplary Simulation
All Patients Stayed on Treatment	2%
BAFTA Rates (5-year decline)	-1%
BAFTA Rates (1 st two year averaged)	-31%
Reduce CHADS ₂ stroke rate by 10%	-2%
Increase ATRIA Bleed Rates by 10%	-3%
Reduce relative risk of stroke for aspirin vs. warfarin by 10%	8%
Reduce relative risk of bleed for aspirin vs. warfarin by 10%	-2%

[0324] The sensitivity analyses of the exemplary simulation of Example 13 showed that a scenario in which all patients stayed on treatment over time in the absence of events resulted in an additional 733 patients (2%) being recommended warfarin. The sensitivity analysis also tested warfarin discontinuation rates from the BAFTA study, as described in Mant et al., “Warfarin versus aspirin for stroke prevention in an elderly community population with atrial fibrillation (the Birmingham Atrial Fibrillation Treatment of the Aged Study, BAFTA, Lancet, 370: 493-503 (2007). It was found that using the BAFTA discontinuation data for both aspirin and warfarin switched the recommendation to warfarin for an additional 434 patients (1%). Additional analyses showed that a 10% reduction in the relative risk of stroke with warfarin versus aspirin from 0.48 to 0.43 resulted in 8% (n = 3316) more warfarin recommendations. A 10% increase in the baseline bleeding rate switches 1077 (3%) warfarin patients to aspirin. Reducing the baseline stroke rate by 10% resulted in a 2% (n = 889) reduction in patients recommended for warfarin.

[0325] The invention described and claimed herein is not to be limited in scope by the specific embodiments herein disclosed since these embodiments are intended as illustrations of several aspects of this invention. Any equivalent embodiments are intended to be within the scope of this invention. Indeed, various modifications of the invention in addition to those shown and described herein will become apparent to those skilled in the art from the foregoing description. Such modifications are also intended to fall within the scope of the appended claims. All publications cited herein are incorporated by reference in their entirety.

CLAIMS

1. A method for reducing a patient's risk of bleed under anticoagulant treatment comprising:

(I) determining a cumulative net benefit for each of two or more treatment options using a Markov chain simulation for predicting a cumulative period of life extension and the occurrence of stroke and bleed events during said cumulative period of life extension under a selected treatment option for a cohort of patients, said simulation comprising:

(A) generating a risk profile for the patient based on the patient's medical history, said risk profile comprising:

(1) a health state comprising:

(a) an event condition of said patient, said event condition is selected from a group consisting of: lack of stroke or bleed events, recurrent and non-recurrent stroke events, recurrent and non-recurrent bleed events, and combinations of stroke events and bleed events,

(b) a course of treatment based on said event condition, wherein said course of treatment is selected from the group consisting of: (i) administration of said treatment option at one or more different dosages, (ii) temporary discontinuation of said treatment option, and (iii) permanent discontinuation of said treatment option,

wherein a numerical value of net benefit is associated with the health state, said numerical value corresponds to a period of life extension in said health state predicted by the simulation, reduced by an amount corresponding to said patient's reduction in quality of life arising from the event condition or the course of treatment for the selected treatment option;

(B) assigning a probability for the occurrence of each predicted stroke event under each treatment option by attributing weighted values to two or more stroke risk factors from said patient's medical history, and a probability for the occurrence of each predicted bleed event under the selected treatment option by attributing weighted values to two or more bleed risk factors from said patient's medical history;

(C) assigning at least one subsequent health state for each predicted stroke event and each predicted bleed event based on the event condition of said patient and the course of treatment in the existing health state; and

(D) repeating steps (B) through (C) for a subsequent period of life extension in said subsequent health state until the patient is predicted to die, or at least 98% of said cohort is predicted to die; and

(II) administering to said patient the treatment option that provides the largest cumulative net benefit based on step (I).

2. The method according to claim 1, wherein said patient suffers from atrial fibrillation.
3. The method according to claim 1, wherein said treatment options comprises administration of a drug or biologic product having anticoagulant activities.
4. The method according to claim 3, wherein said drug or biologic product is selected from a group consisting of vitamin K antagonists, antithrombin activators, factor Xa inhibitors, direct thrombin inhibitors, and glycoprotein IIb/IIIa inhibitors.
5. The method according to claim 3, wherein said drug comprises warfarin or aspirin.
6. The method according to claim 4, wherein said drug comprises edoxaban.
7. The method according to claim 3, wherein said treatment options further comprises administration of a second drug or biologic product having anticoagulant activities.
8. The method according to claim 1, wherein said Markov chain simulation comprises Monte Carlo methods.
9. The method according to claim 1, wherein said Markov chain simulation comprises expected value analysis.
10. The method according to claim 1, wherein the size of said cohort is at least 500.
11. The method according to claim 10, wherein the size of said cohort is at least 1,000.
12. The method according to claim 11, wherein the size of said cohort is at least 5,000.

13. The method according to claim 12, wherein the size of said cohort is at least 10,000.
14. The method according to claim 1, wherein step (D) is repeated until the patient is predicted to die, or at least 99% of said cohort is predicted to die.
15. The method according to claim 14, wherein step (D) is repeated until the patient is predicted to die, or at least 99.9% of said cohort is predicted to die.
16. The method according to claim 1, wherein step (D) is repeated until the patient is predicted to die, or substantially all of said cohort is predicted to die.
17. The method according to claim 1, wherein said net benefit is quantified in quality adjusted life years (QALYs), overall cost, number needed to treat (NNT), total number of hemorrhagic or embolic events, hospital days, total hemorrhagic and/or embolic strokes, total number of major events, or a combination thereof.
18. The method according to claim 17, wherein said net benefit is quantified in QALYs.
19. The method according to claim 1, wherein said predicted stroke event is selected from a group consisting of fatal ischemic strokes, severe ischemic strokes, mild ischemic strokes, and reversible ischemic strokes.
20. The method according to claim 1, wherein said predicted bleed event is selected from a group consisting of fatal hemorrhages, intra-cranial hemorrhages, major non-cranial hemorrhages, gastrointestinal hemorrhages, and minor hemorrhages.
21. The method according to claim 1, wherein at least one stroke risk factor is selected from the group consisting of prior stroke or prior transient ischemic attack (TIA), age, hypertension, diabetes mellitus, and heart failure.
22. The method according to claim 1, wherein at least one bleed risk factor is selected from the group consisting of anemia, age, history of bleeding, reduced level of estimated glomerular filtration rate (eGFR), and history of hypertension.
23. The method according to claim 1, wherein said simulation iterates every 1 year of life predicted.

24. The method according to claim 1, wherein said simulation iterates every 6 months of life predicted.

25. The method according to claim 1, wherein said simulation iterates every 3 months of life predicted.

26. The method according to claim 1, wherein said simulation iterates every 1 month of life predicted.

27. The method according to claim 1, wherein said probability for the occurrence of each predicted stroke event under each treatment is derived from a database of historic medical history data.

28. The method according to claim 1, wherein said probability for the occurrence of each predicted bleed event under each treatment is derived from a database of historic medical history data.

29. A method for reducing a patient's risk of bleed under anticoagulant treatment comprising:

(I) determining a cumulative net benefit for each of two or more treatment options using a Markov chain simulation for predicting a cumulative period of life extension and the occurrence of stroke and bleed events during said cumulative period of life extension under a selected treatment option for a cohort of patients, said simulation comprising:

(A) generating a risk profile for the patient based on the patient's medical history, said risk profile comprising:

(1) a health state comprising:

(a) an event condition of said patient, said event condition is selected from a group consisting of: lack of stroke or bleed events, recurrent and non-recurrent stroke events, recurrent and non-recurrent bleed events, and combinations of stroke events and bleed events,

(b) a course of treatment based on said event condition, wherein said course of treatment is selected from the group consisting of: (i) administration

of said treatment option at one or more different dosages, (ii) temporary discontinuation of said treatment option, and (iii) permanent discontinuation of said treatment option,

(c) a first risk score attributing weighted values to two or more stroke risk factors from said patient's medical history, and

(d) a second risk score attributing weighted values to two or more stroke bleed factors from said patient's medical history,

wherein a numerical value of net benefit is associated with the health state, said numerical value corresponds to a period of life extension in said health state predicted by the simulation, reduced by an amount corresponding to said patient's reduction in quality of life arising from the event condition or the course of treatment for the selected treatment option;

(B) assigning a probability for the occurrence of each predicted stroke event under each treatment option corresponding to said first risk score and a probability for the occurrence of each predicted bleed event corresponding to said the second risk score;

(C) assigning at least one subsequent health state for each predicted stroke event and each predicted bleed event based on the condition of said patient and the course of treatment in the existing health state; and

(D) repeating steps (B) through (C) for a subsequent period of life extension in said subsequent health state until the patient is predicted to die, or at least 98% of said cohort is predicted to die; and

(II) administering to said patient the treatment option that provides the largest cumulative net benefit based on step (I).

27. The method according to claim 26, wherein at least one stroke risk factor is selected from the group consisting of prior stroke or prior transient ischemic attack (TIA), age, hypertension, diabetes mellitus, and heart failure.
28. The method according to claim 27, wherein said first risk score attributes a weighted value of 2 to a prior stroke or prior transient ischemic attack (TIA), and a weighted value of 1 to at least one other stroke risk factor.
29. The method according to claim 26, wherein at least one bleed risk factor is selected from the group consisting of anemia, age, history of bleeding, reduced level of estimated glomerular filtration rate (eGFR), and history of hypertension.
30. The method according to claim 29, wherein said second risk score attributes a weighted value of 3 to anemia and a weighted value of either 1 or 2 to at least one other bleed risk factor.
31. The method according to claim 30, wherein said second risk score attributes a weighted value of 2 to a second bleed risk factor selected from the group consisting of age, history of bleeding, and reduced level of estimated glomerular filtration rate (eGFR).
32. The method according to claim 30, wherein said second risk score attributes a weighted value of 1 to history of hypertension.
33. A method for treating atrial fibrillation comprising:
- (I) determining a cumulative net benefit for each of two or more treatment options using a Markov chain simulation for predicting a cumulative period of life extension and the occurrence of stroke and bleed events during said cumulative period of life extension under a selected treatment option for a cohort of patients, said simulation comprising:
 - (A) generating a risk profile for the patient based on the patient's medical history, said risk profile comprising:
 - (1) a health state comprising:
 - (a) an event condition of said patient, said event condition is selected from a group consisting of: lack of stroke or bleed events, recurrent and non-

recurrent stroke events, recurrent and non-recurrent bleed events, and combinations of stroke events and bleed events,

(b) a course of treatment based on said event condition, wherein said course of treatment is selected from the group consisting of: (i) administration of said treatment option at one or more different dosages, (ii) temporary discontinuation of said treatment option, and (iii) permanent discontinuation of said treatment option,

wherein a numerical value of net benefit is associated with the health state, said numerical value corresponds to a period of life extension in said health state predicted by the simulation, reduced by an amount corresponding to said patient's reduction in quality of life arising from the event condition or the course of treatment for the selected treatment option;

(B) assigning a probability for the occurrence of each predicted stroke event under each treatment option by attributing weighted values to two or more stroke risk factors from said patient's medical history, and a probability for the occurrence of each predicted bleed event under the selected treatment option by attributing weighted values to two or more bleed risk factors from said patient's medical history;

(C) assigning at least one subsequent health state for each predicted stroke event and each predicted bleed event based on the event condition of said patient and the course of treatment in the existing health state; and

(D) repeating steps (B) through (C) for a subsequent period of life extension in said subsequent health state until the patient is predicted to die, or at least 98% of said cohort is predicted to die; and

(II) administering to said patient the treatment option that provides the largest cumulative net benefit based on step (I).

34. A computer program product, comprising a computer usable medium having a computer readable program code embodied therein, said computer readable program code adapted to be executed to implement a method for displaying an output to a user, said method comprising:

(A) providing a system, wherein the system comprises distinct software modules, and wherein the distinct software modules comprises a logic processing module, a Markov chain simulation module, and a user-interface for receiving input from said user and providing said output to said user,

(B) obtaining, by the user-interface, from said user an input of the patient's medical history or from a remote database an electronic medical record for said patient;

(C) parsing, by the logic processing module, the input from the user or the electronic medical record into a risk profile for the patient, said profile comprising:

(1) a health state comprising:

(a) an event condition of said patient, said event condition is selected from a group consisting of: lack of stroke or bleed events, recurrent and non-recurrent stroke events, recurrent and non-recurrent bleed events, and combinations of stroke events and bleed events,

(b) a course of treatment based on said event condition, wherein said course of treatment is selected from the group consisting of: (i) administration of an anticoagulant treatment option at one or more different dosages, (ii) temporary discontinuation of said treatment option, and (iii) permanent discontinuation of said treatment option,

wherein a numerical value of net benefit is associated with the health state, said numerical value corresponds to a period of life extension in said health state predicted by the simulation, reduced by an amount corresponding to said patient's reduction in quality of life arising from the event condition or the course of treatment for the treatment option;

(D) automatically assigning, by the Markov chain simulation module in response to being called by the logic processing module:

(1) a probability for the occurrence of each predicted stroke event under each treatment option by attributing weighted values to two or more stroke risk factors from said patient's medical history, and a probability for the occurrence of each predicted

bleed event under the selected treatment option by attributing weighted values to two or more bleed risk factors from said patient's medical history, and

(2) at least one subsequent health state for each predicted stroke event and each predicted bleed event based on the event condition of said patient and the course of treatment in the existing health state; and

(E) simulating a cohort of patients by automatically repeating step (D) for a subsequent period of life extension in said subsequent health state until the patient is predicted to die, or at least 98% of said cohort is predicted to die, and determining a cumulative net benefit for said treatment option, wherein said simulating is performed by the Markov chain simulation module in response to being called by the logic processing module;

(F) displaying, by the user interface, said cumulative net benefit for said treatment option to said user.

35. The computer program product according to claim 34, wherein step (D) is repeated until the patient is predicted to die, or at least 99% of said cohort is predicted to die.

36. The computer program product according to claim 35, wherein step (D) is repeated until the patient is predicted to die, or at least 99.9% of said cohort is predicted to die.

37. The computer program product according to claim 34, wherein step (D) is repeated until the patient is predicted to die, or substantially all of said cohort is predicted to die.

38. A computer program product, comprising a computer usable medium having a computer readable program code embodied therein, said computer readable program code adapted to be executed to implement a method for displaying a selection of among two or more anticoagulant treatment options to a user, said method comprising:

(A) providing a system, wherein the system comprises distinct software modules, and wherein the distinct software modules comprises a logic processing module, a Markov chain simulation module, and a user-interface for receiving input from said user and providing said output to said user,

(B) obtaining, by the user-interface, from said user an input of the patient's medical history or from a remote database an electronic medical record for said patient;

(C) parsing, by the logic processing module, the input from the user or the electronic medical record into a risk profile under each anticoagulant treatment option for the patient, said profile comprising:

(1) a health state comprising:

(a) an event condition of said patient, said event condition is selected from a group consisting of: lack of stroke or bleed events, recurrent and non-recurrent stroke events, recurrent and non-recurrent bleed events, and combinations of stroke events and bleed events,

(b) a course of treatment based on said event condition, wherein said course of treatment is selected from the group consisting of: (i) administration of an anticoagulant treatment option at one or more different dosages, (ii) temporary discontinuation of said treatment option, and (iii) permanent discontinuation of said treatment option,

wherein a numerical value of net benefit is associated with the health state, said numerical value corresponds to a period of life extension in said health state predicted by the simulation, reduced by an amount corresponding to said patient's reduction in quality of life arising from the event condition or the course of treatment for the treatment option;

(D) automatically assigning, by the Markov chain simulation module in response to being called by the logic processing module:

(1) a probability for the occurrence of each predicted stroke event under each treatment option by attributing weighted values to two or more stroke risk factors from said patient's medical history, and a probability for the occurrence of each predicted bleed event under the selected treatment option by attributing weighted values to two or more bleed risk factors from said patient's medical history, and

(2) at least one subsequent health state for each predicted stroke event and each predicted bleed event based on the event condition of said patient and the course of treatment in the existing health state; and

(E) simulating a computer generated cohort of patients by automatically repeating step (D) for a subsequent period of life extension in said subsequent health state until the patient is predicted to die, or at least 98% of said cohort is predicted to die, and determining a cumulative net benefit for each treatment option, wherein said simulating is performed by the Markov chain simulation module in response to being called by the logic processing module;

(F) choosing, by the logic processing module, selecting the treatment option that provides the largest benefit based on step (F) among said two or more anticoagulant treatment options; and

(G) displaying, by the user interface, the selected treatment option from step (F).

39. The computer program product according to claim 38, wherein step (D) is repeated until the patient is predicted to die, or at least 99% of said cohort is predicted to die.

40. The computer program product according to claim 39, wherein step (D) is repeated until the patient is predicted to die, or at least 99.9% of said cohort is predicted to die.

41. The computer program product according to claim 38, wherein step (D) is repeated until the patient is predicted to die, or substantially all of said cohort is predicted to die.

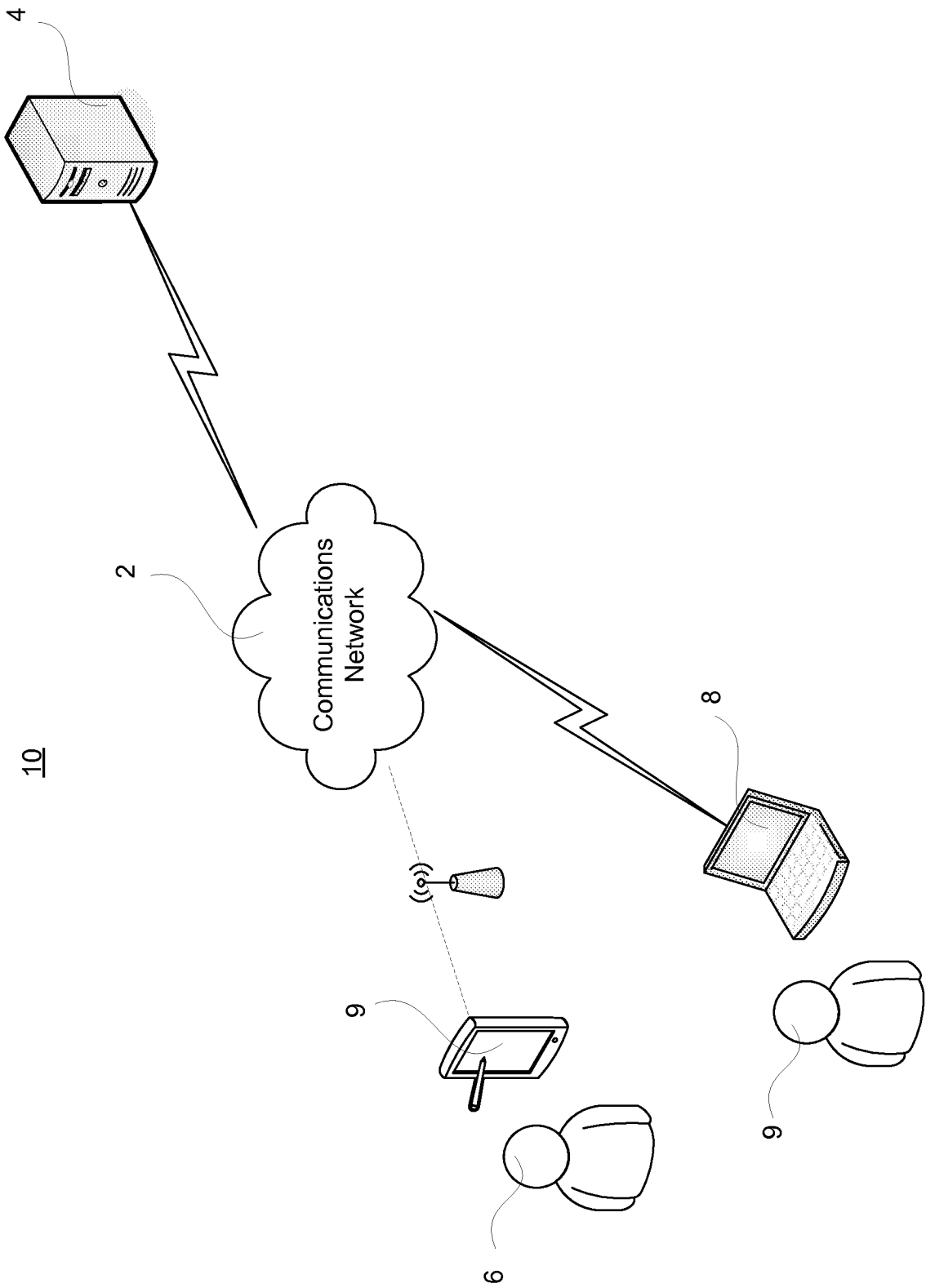


Fig. 1

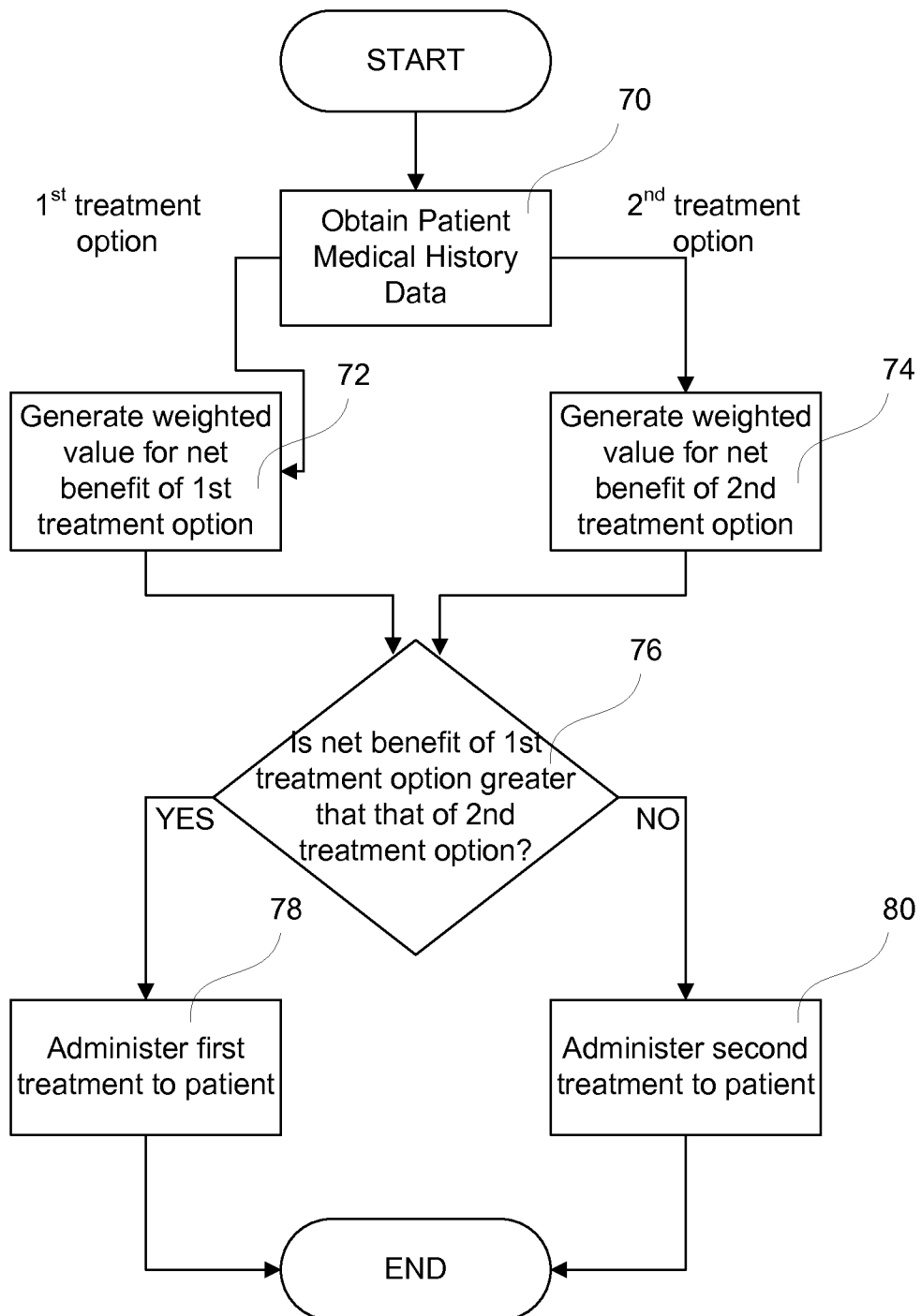


Fig. 2

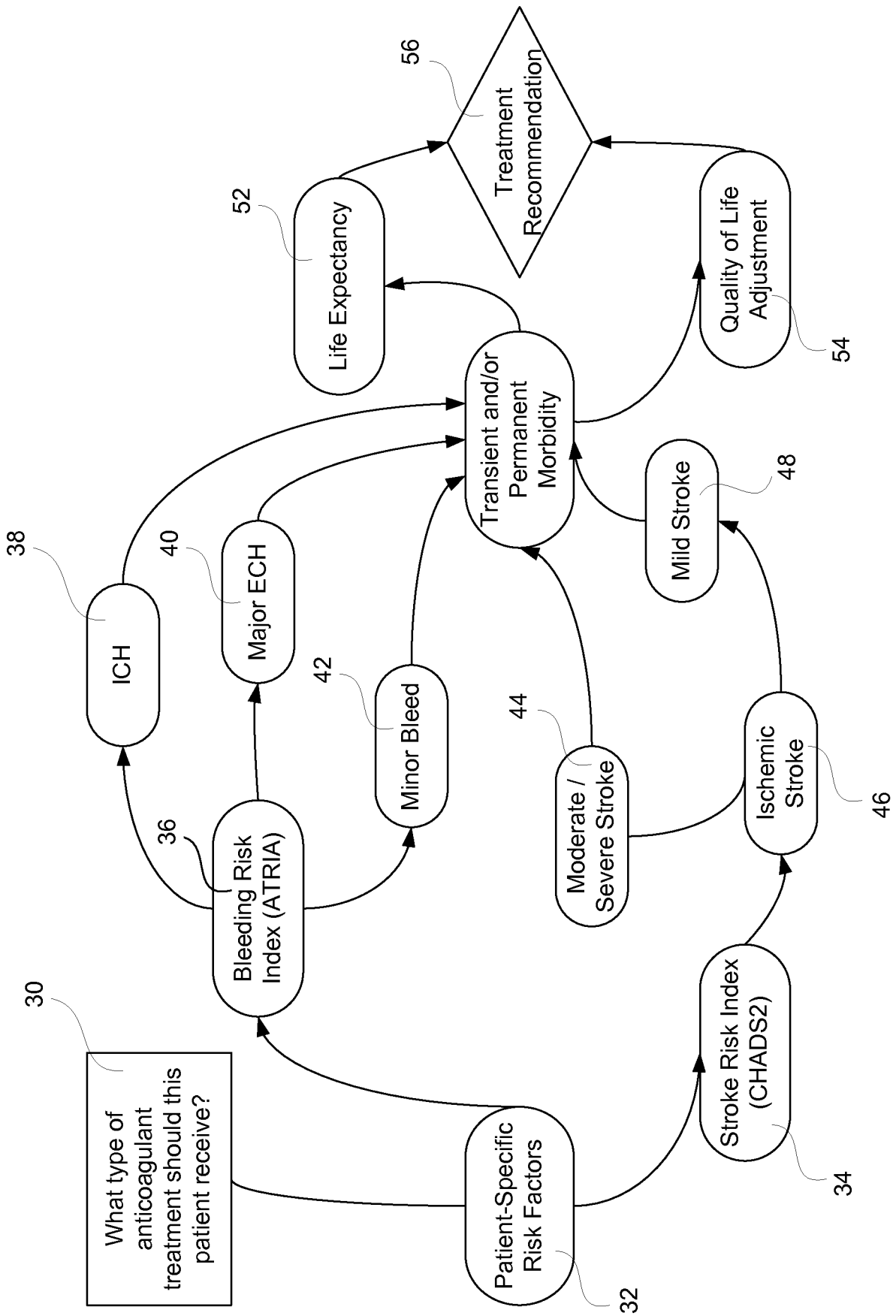


Fig. 3

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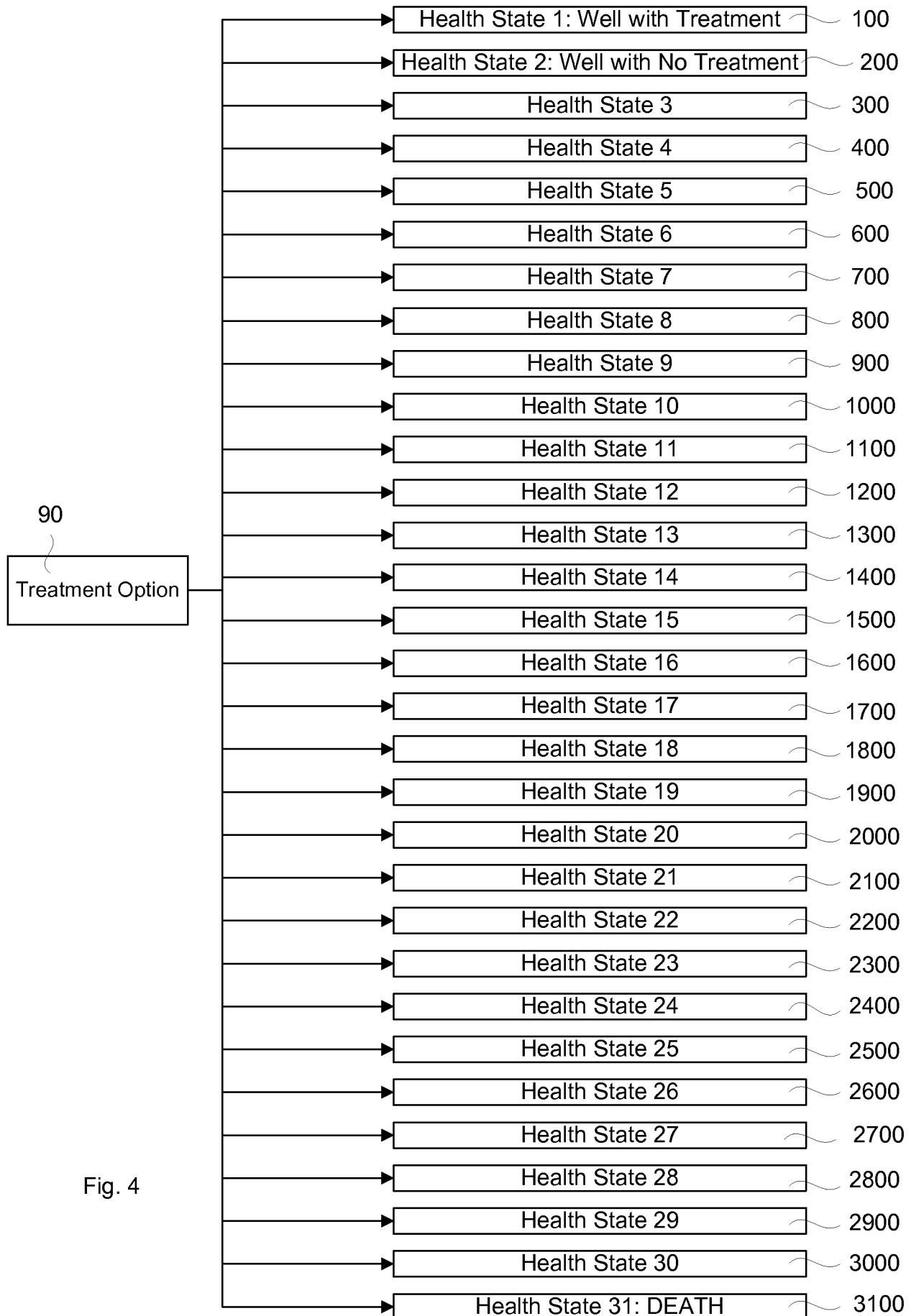


Fig. 4

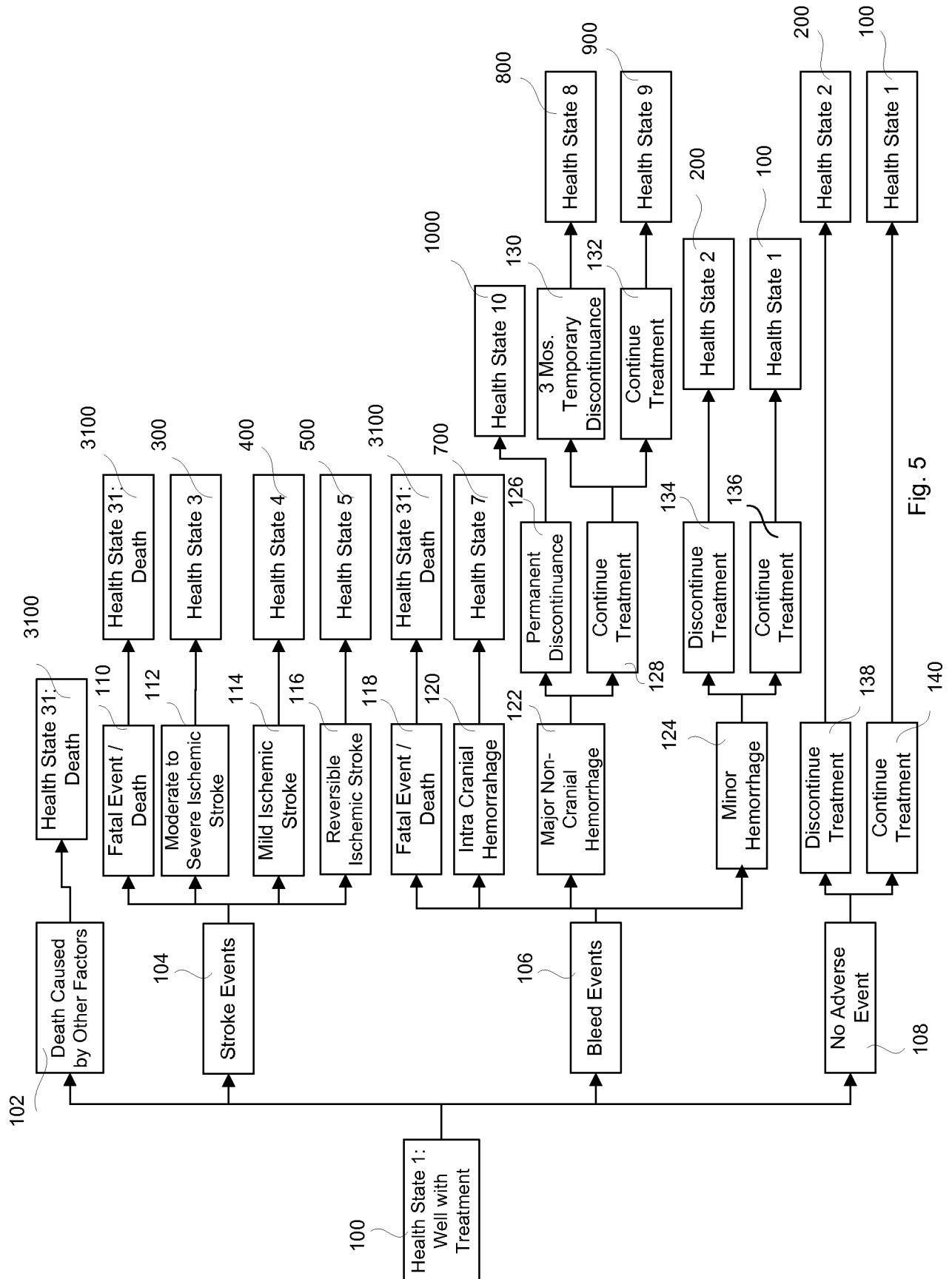
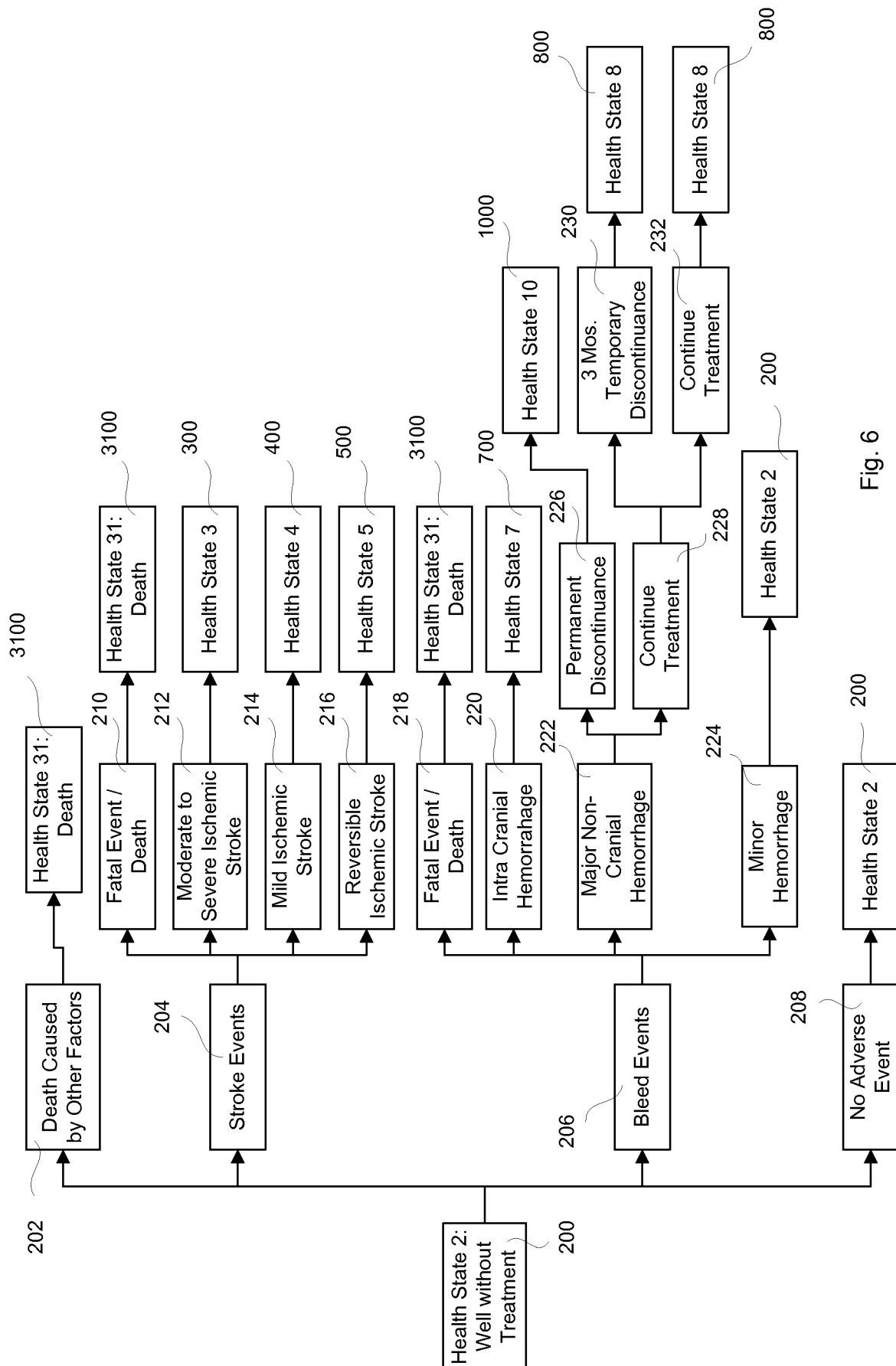


Fig. 5



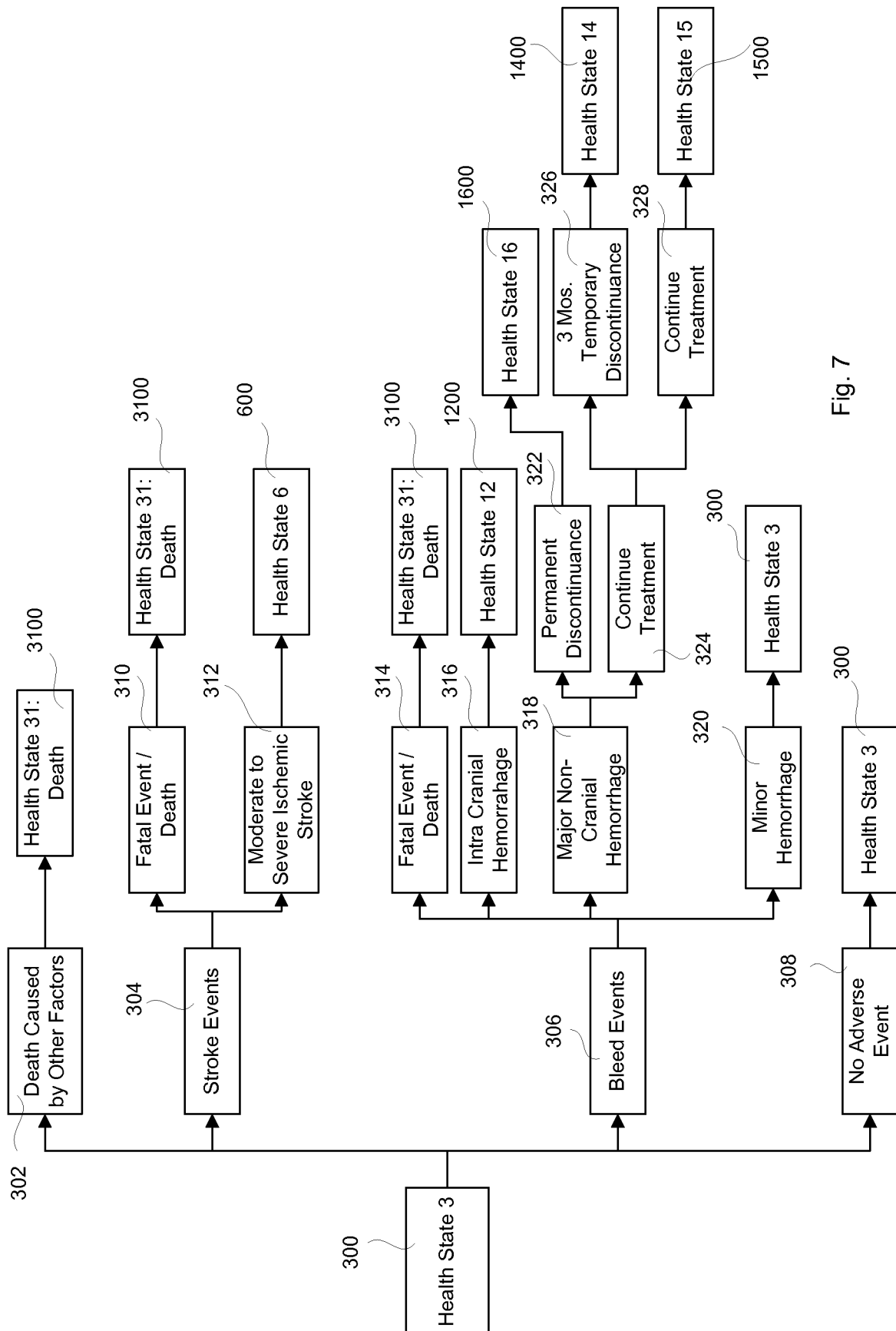


Fig. 7

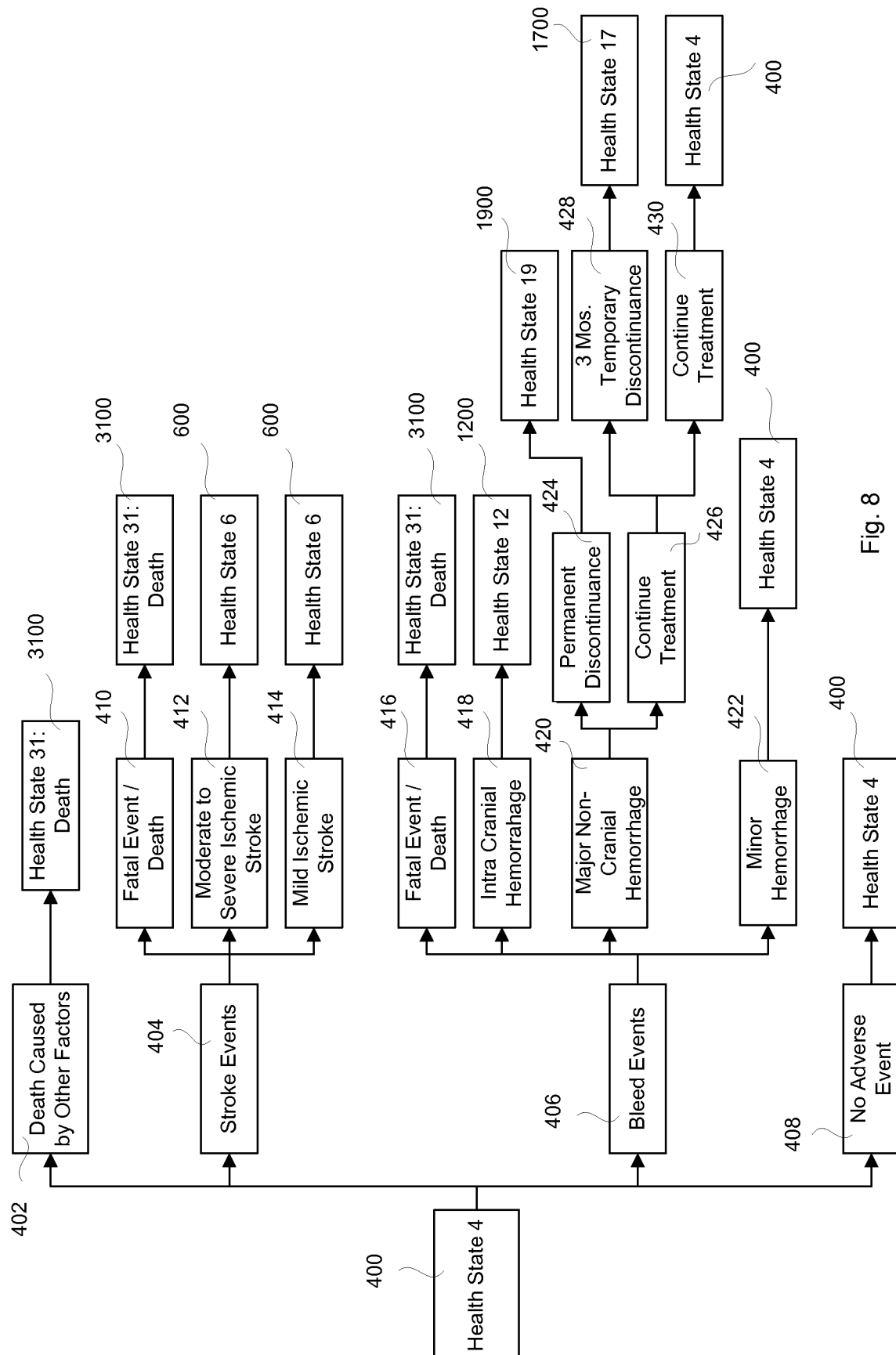


Fig. 8

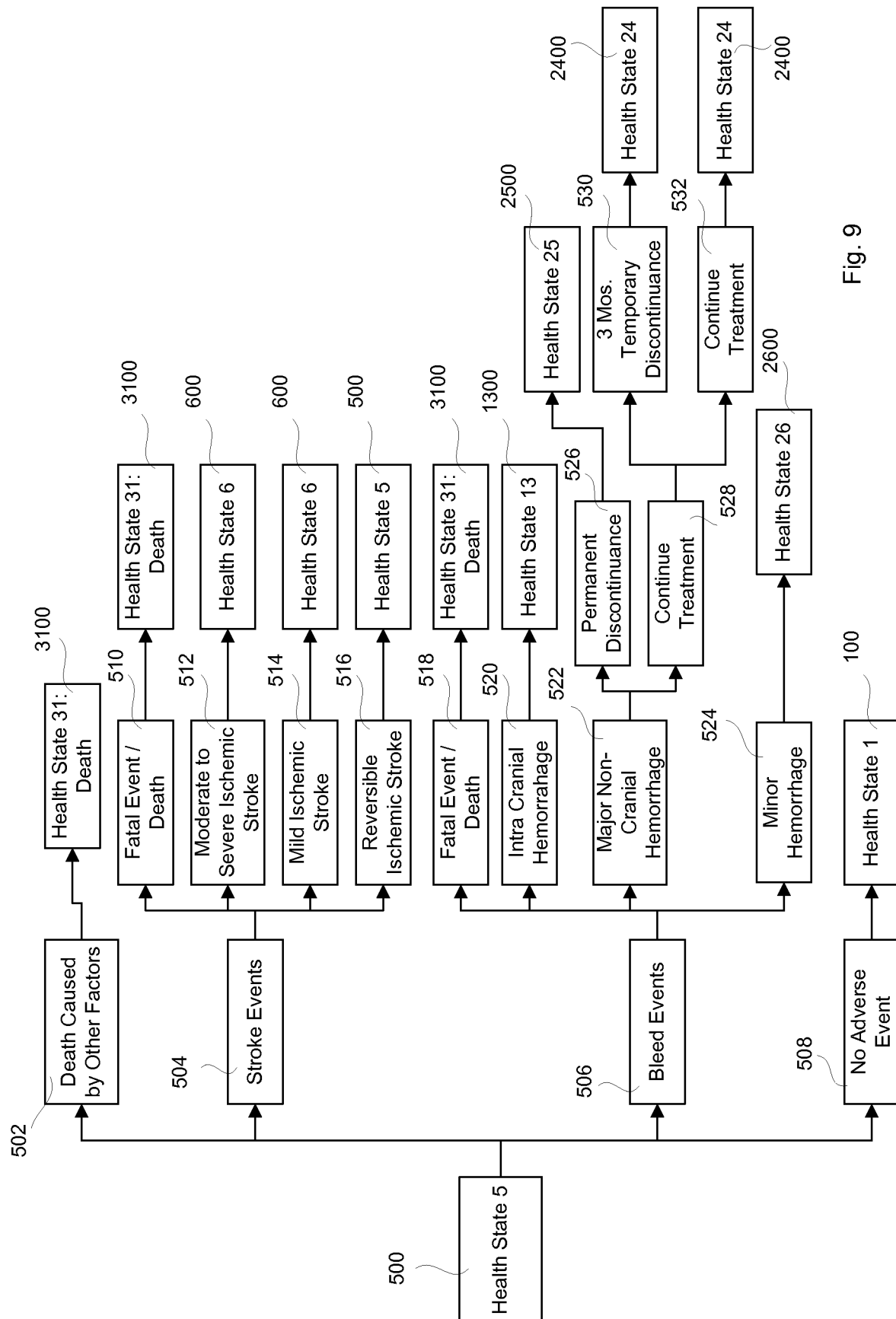


Fig. 9

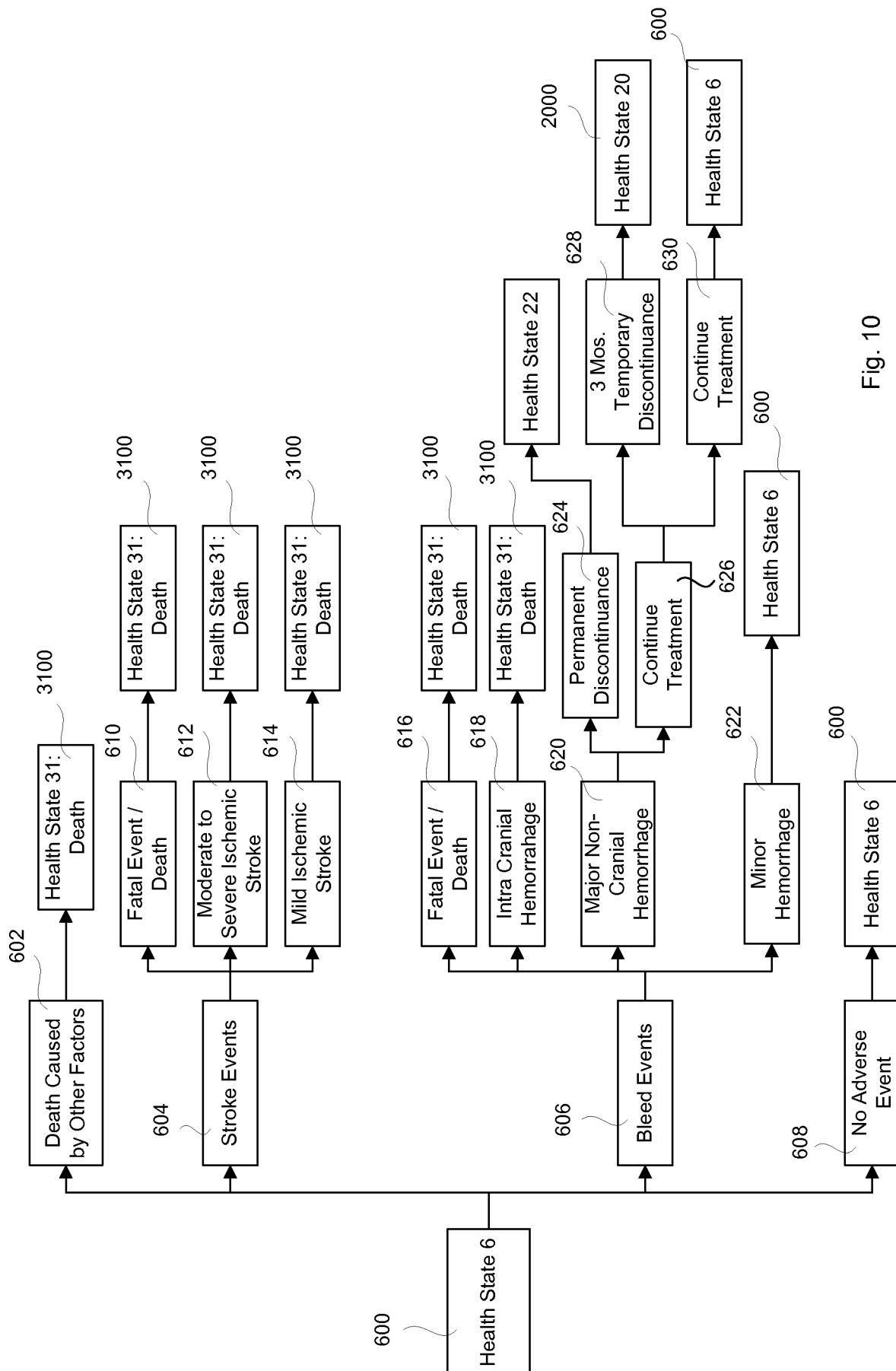


Fig. 10

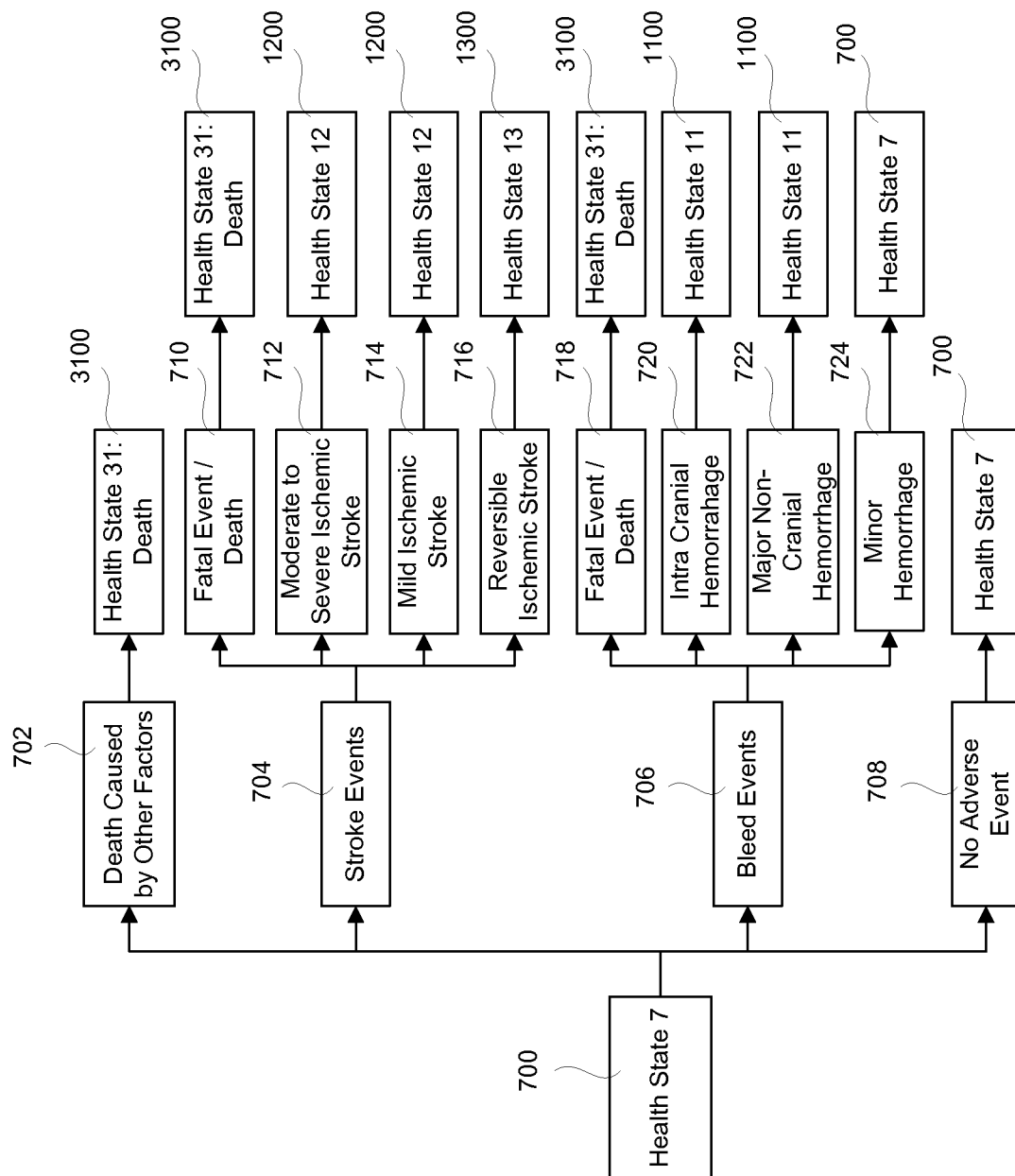


Fig. 11

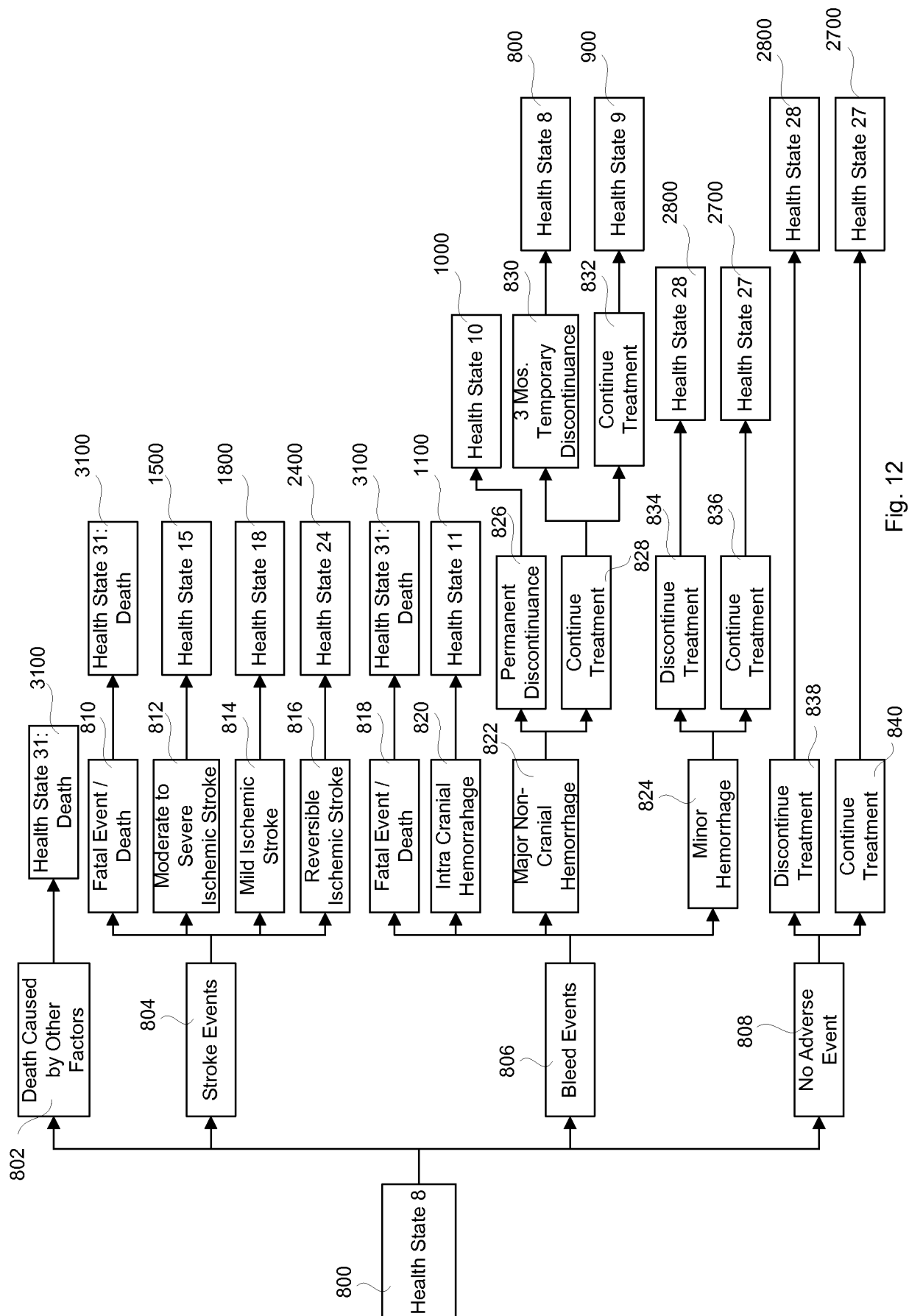


Fig. 12

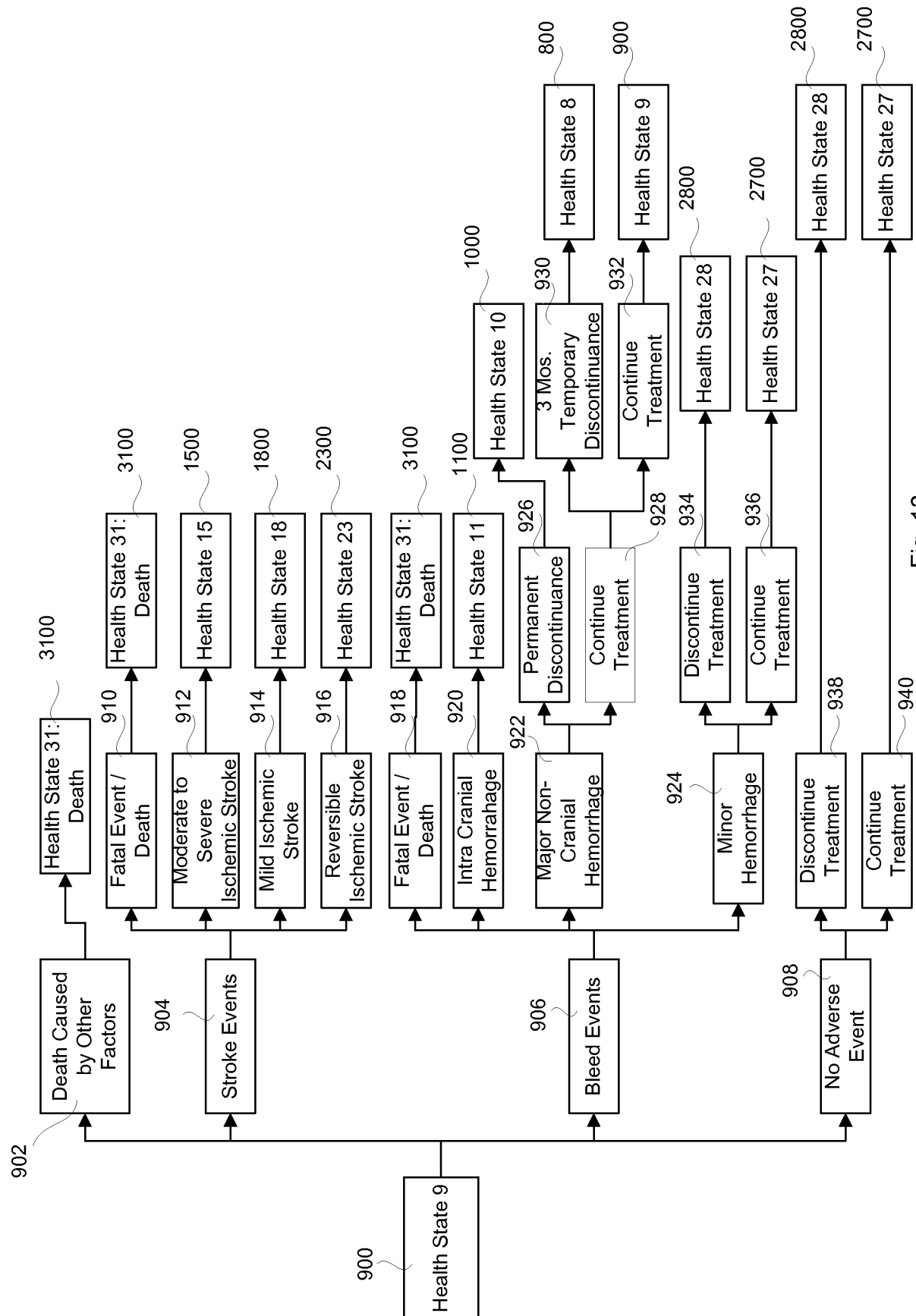


Fig. 13

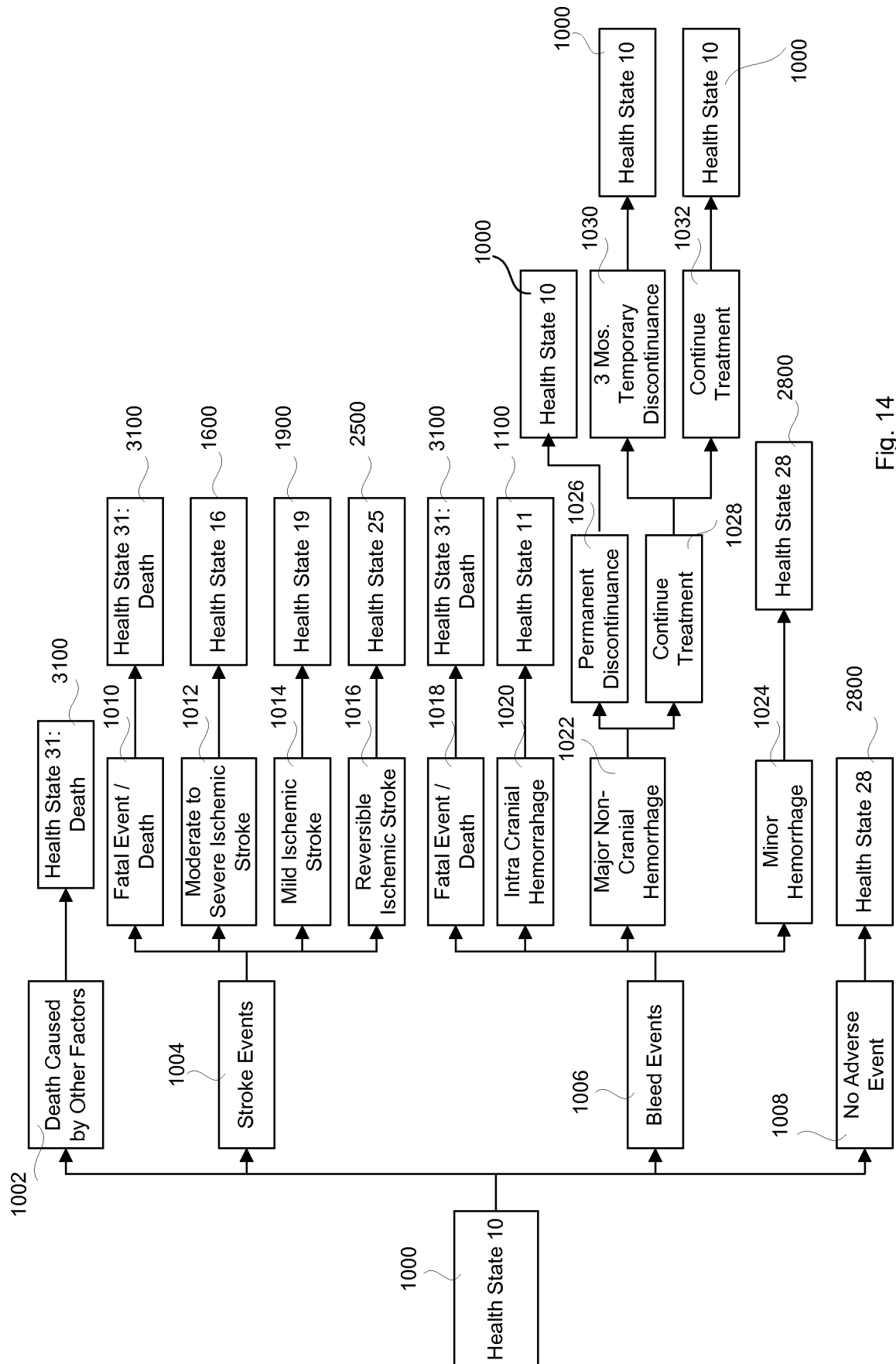


Fig. 14

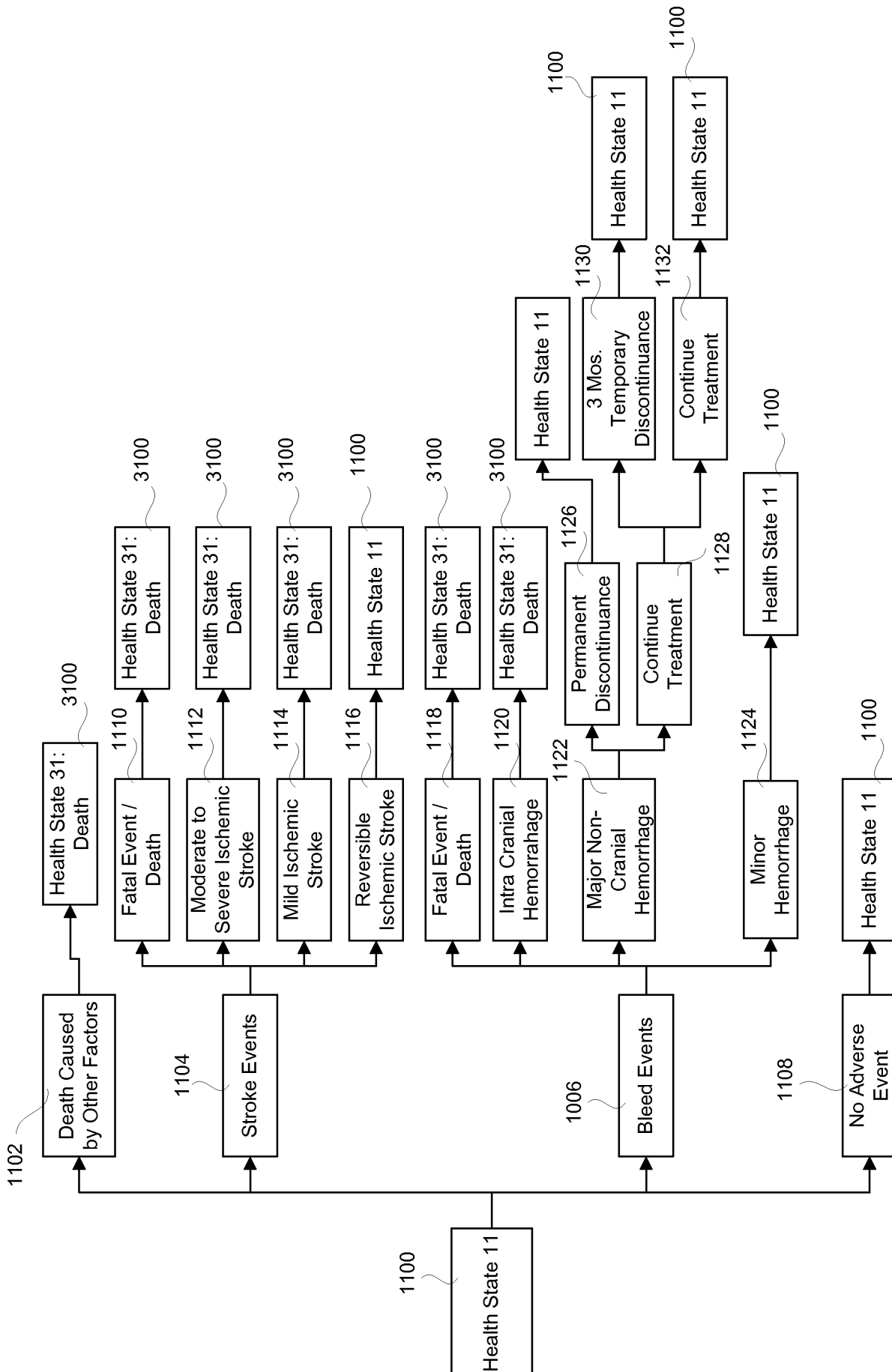


Fig. 15

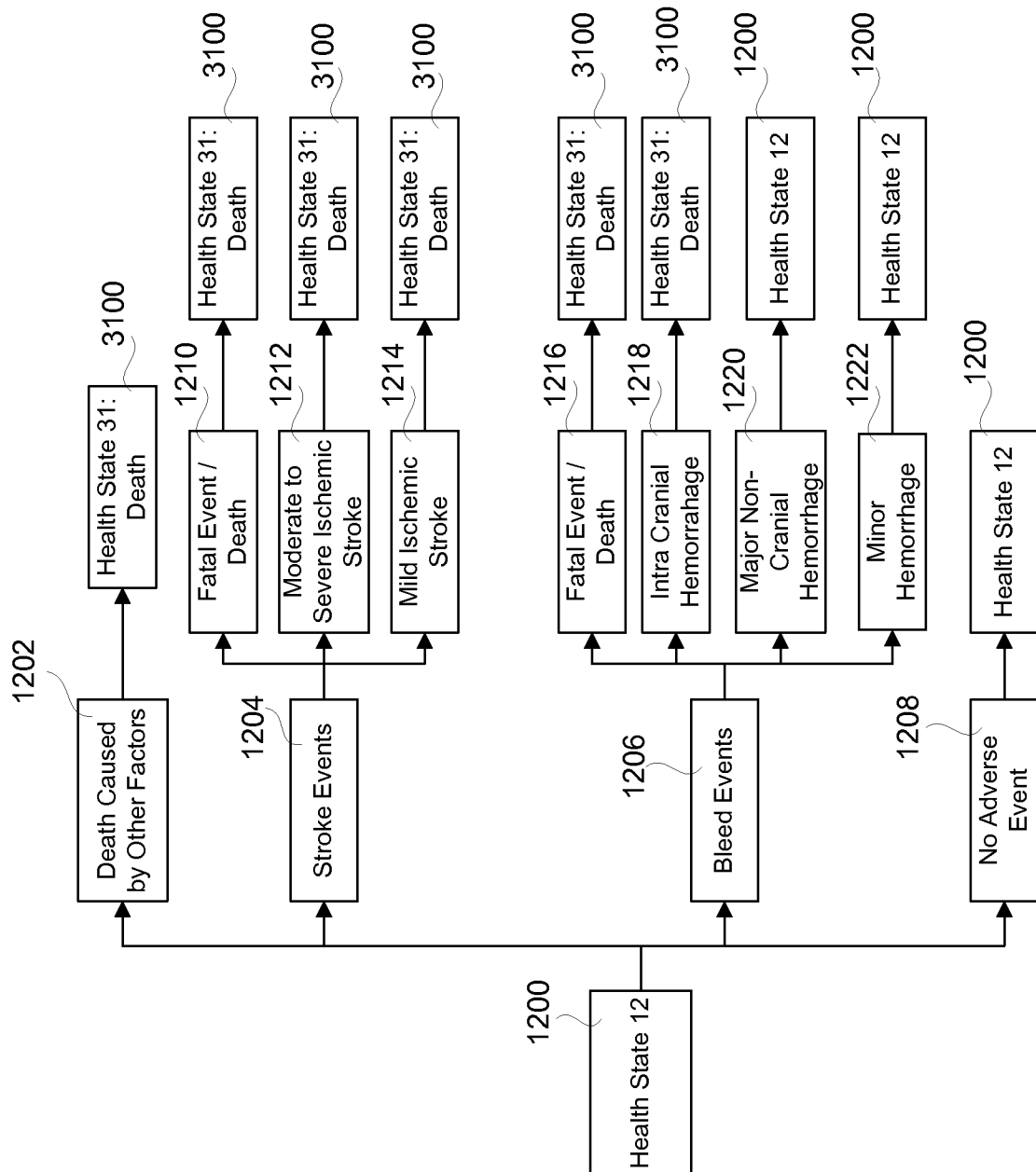


Fig. 16

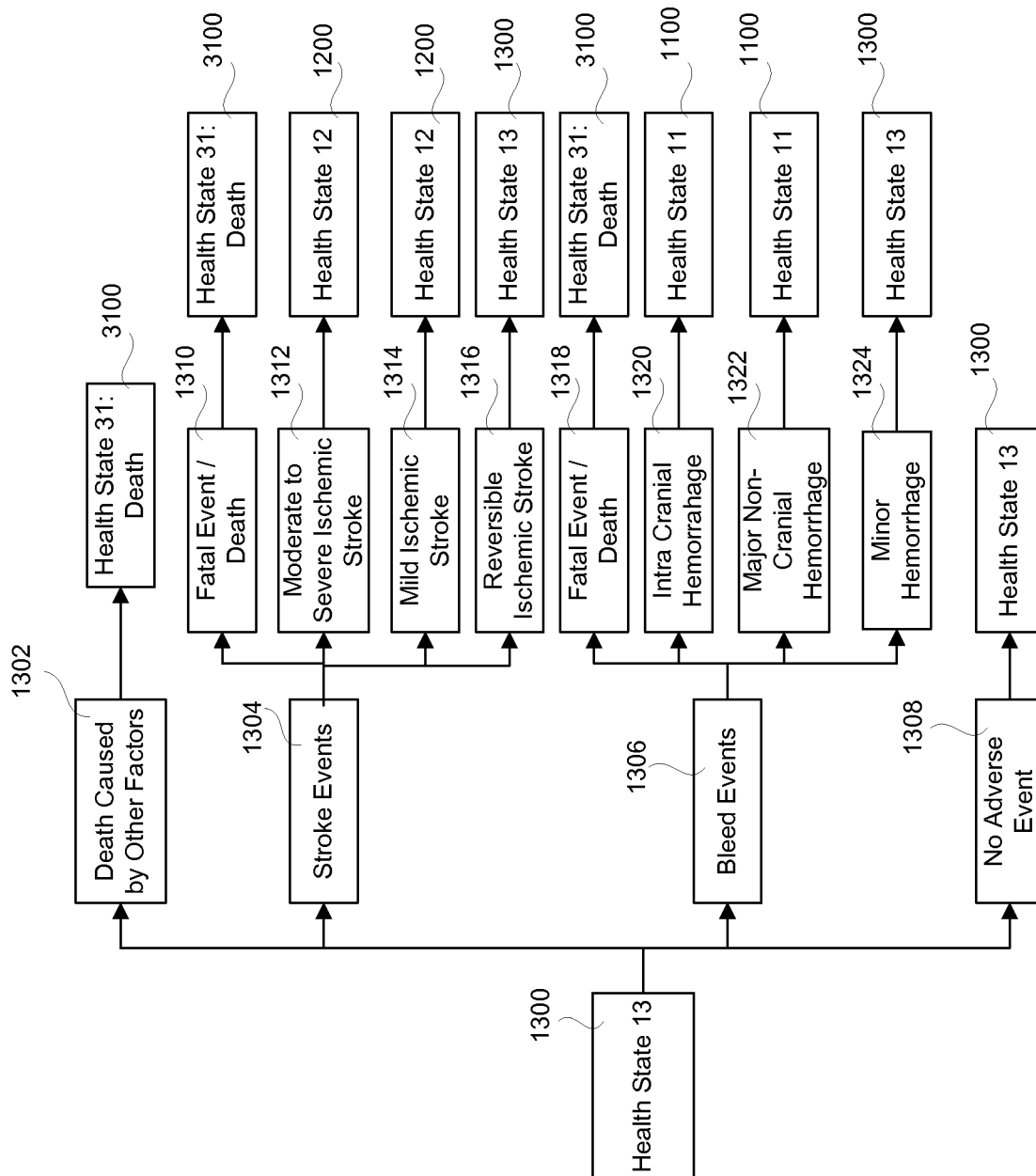


Fig. 17

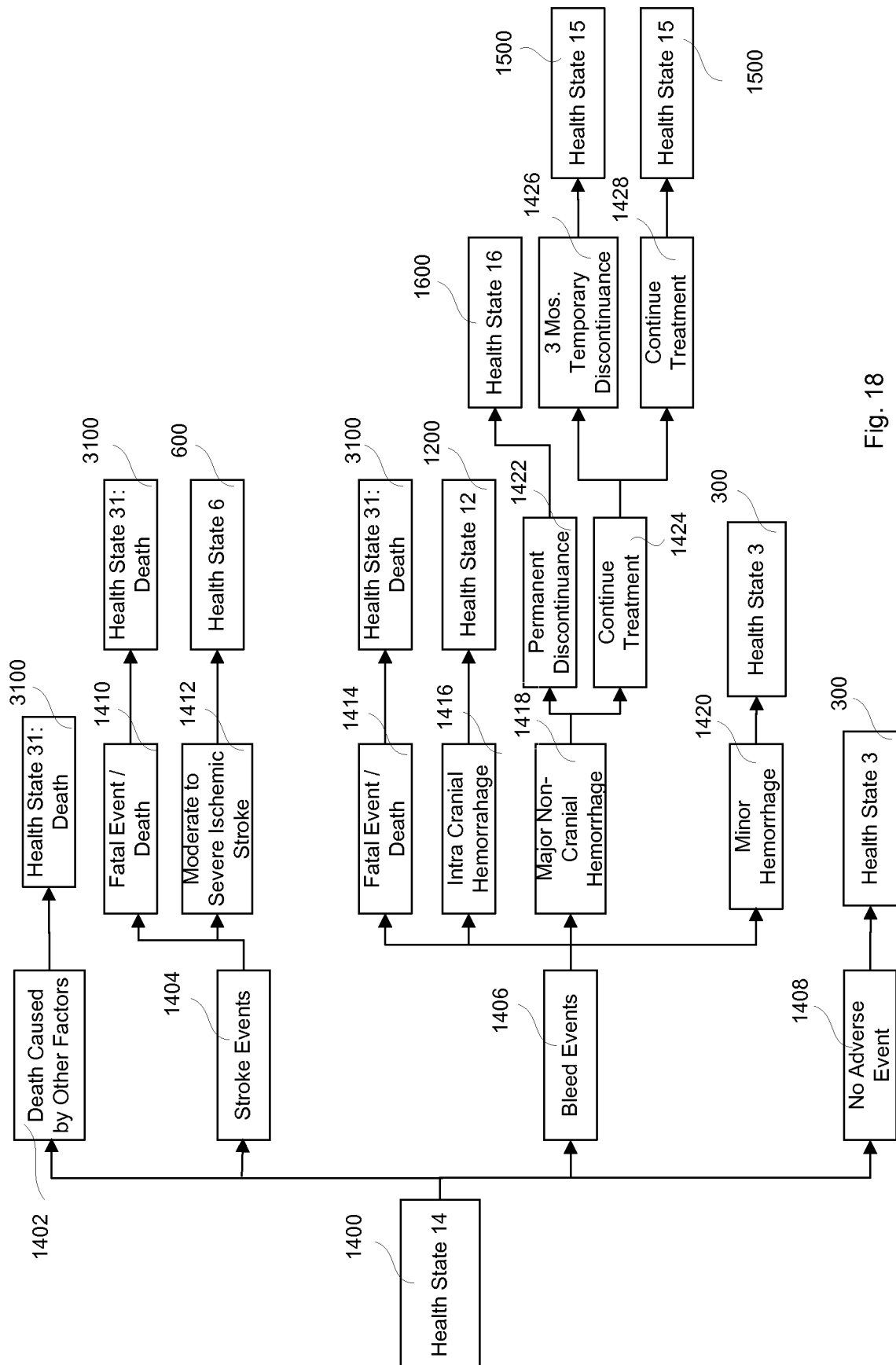


Fig. 18

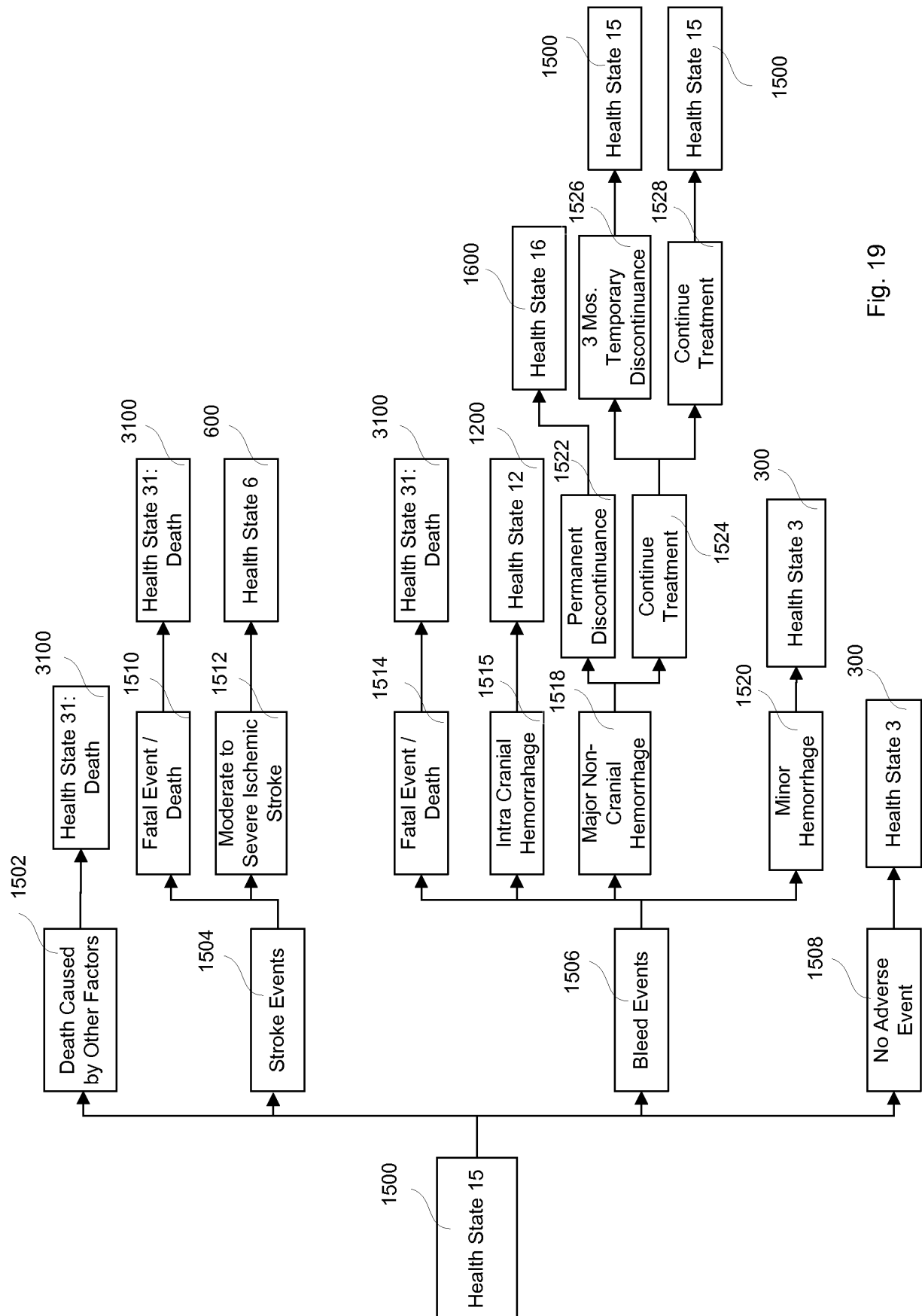


Fig. 19

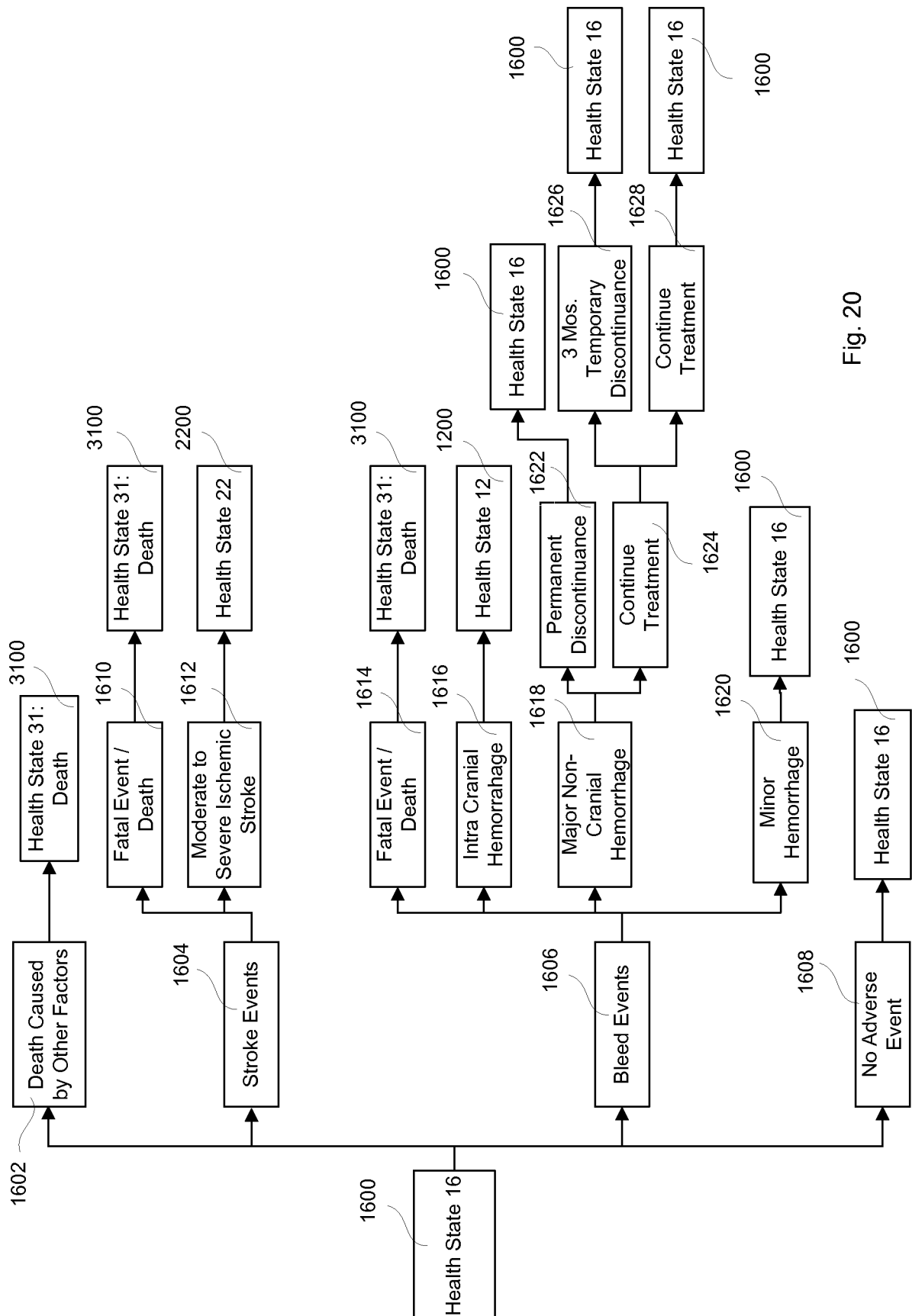


Fig. 20

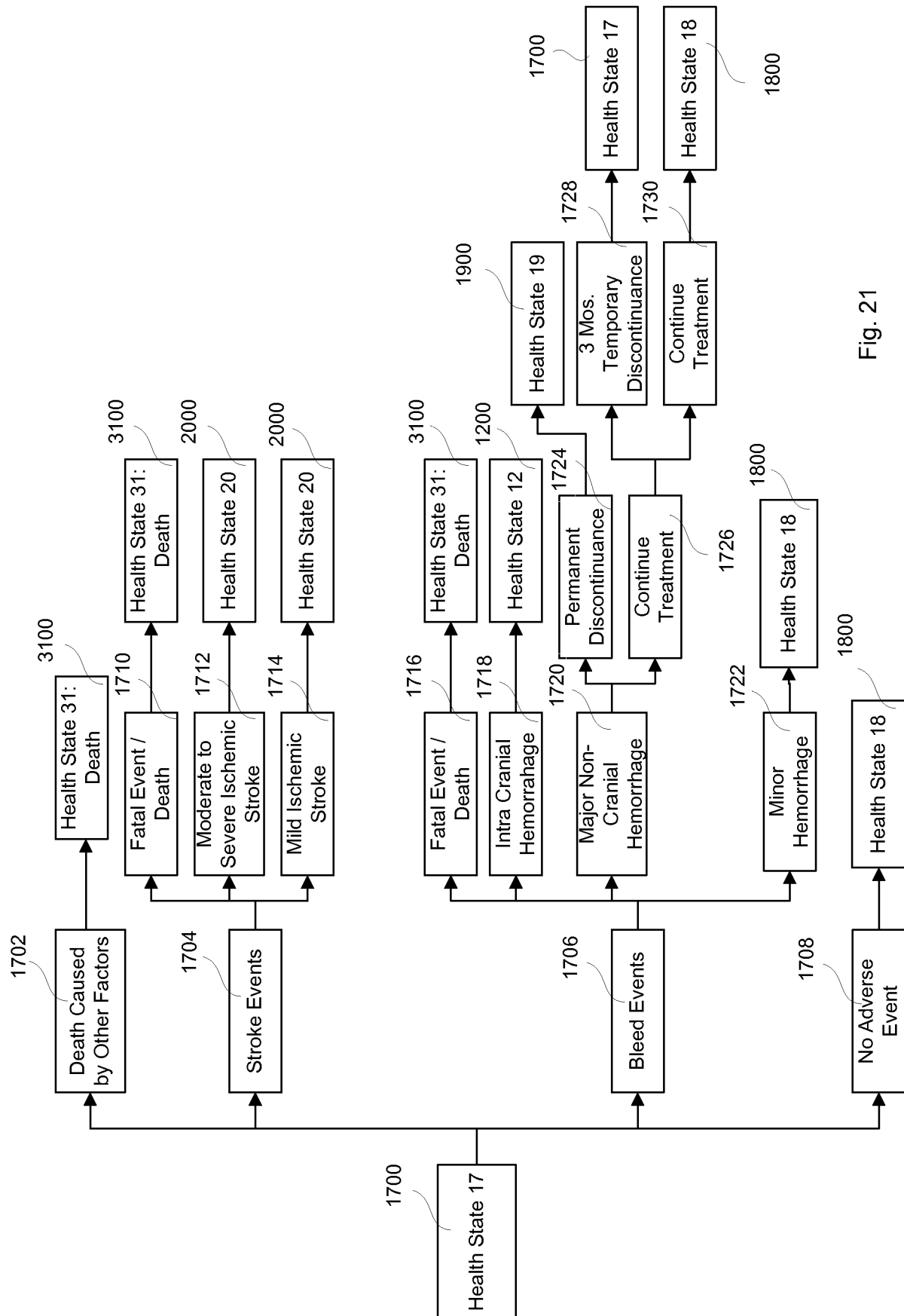


Fig. 21

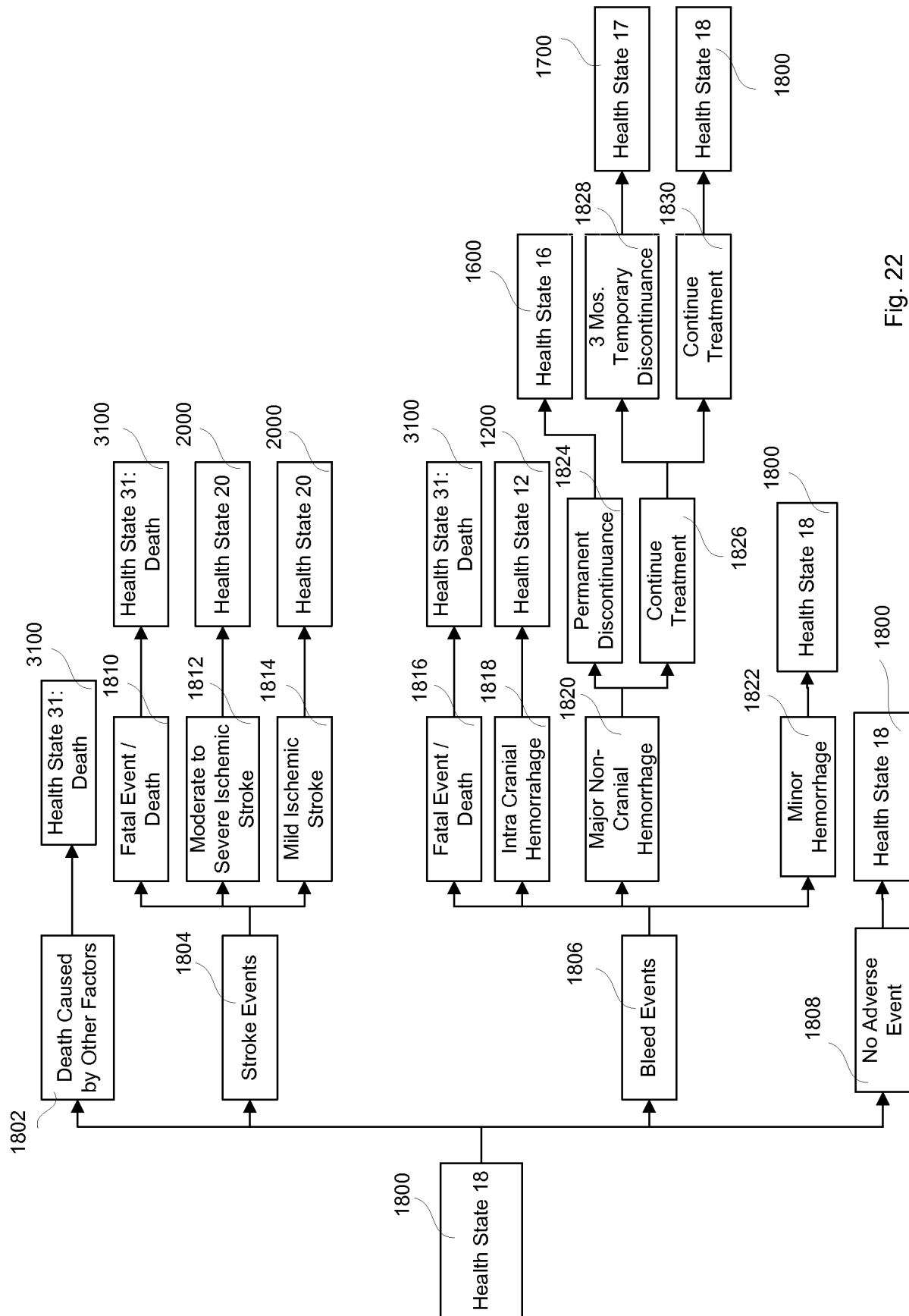


Fig. 22

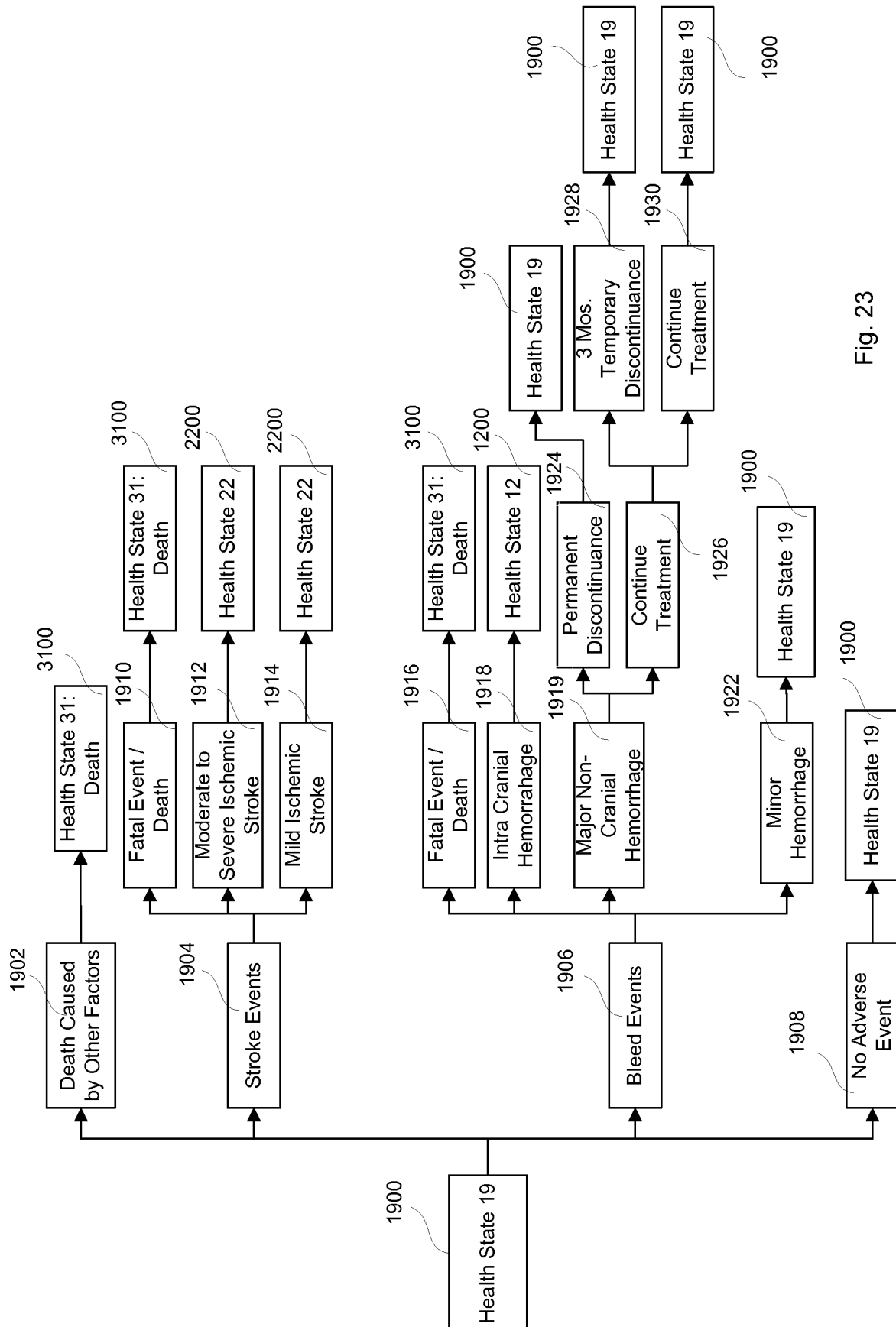


Fig. 23

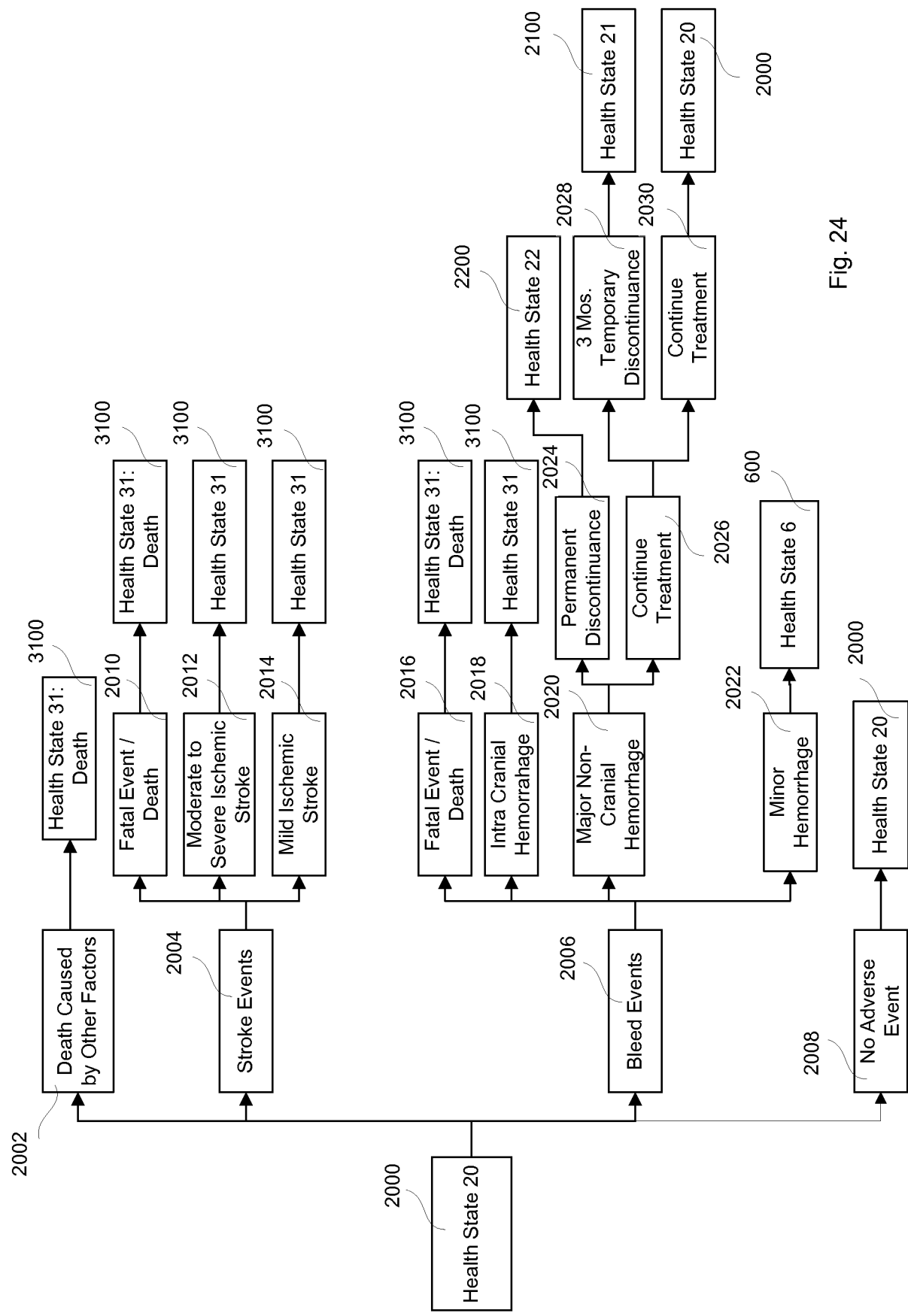


Fig. 24

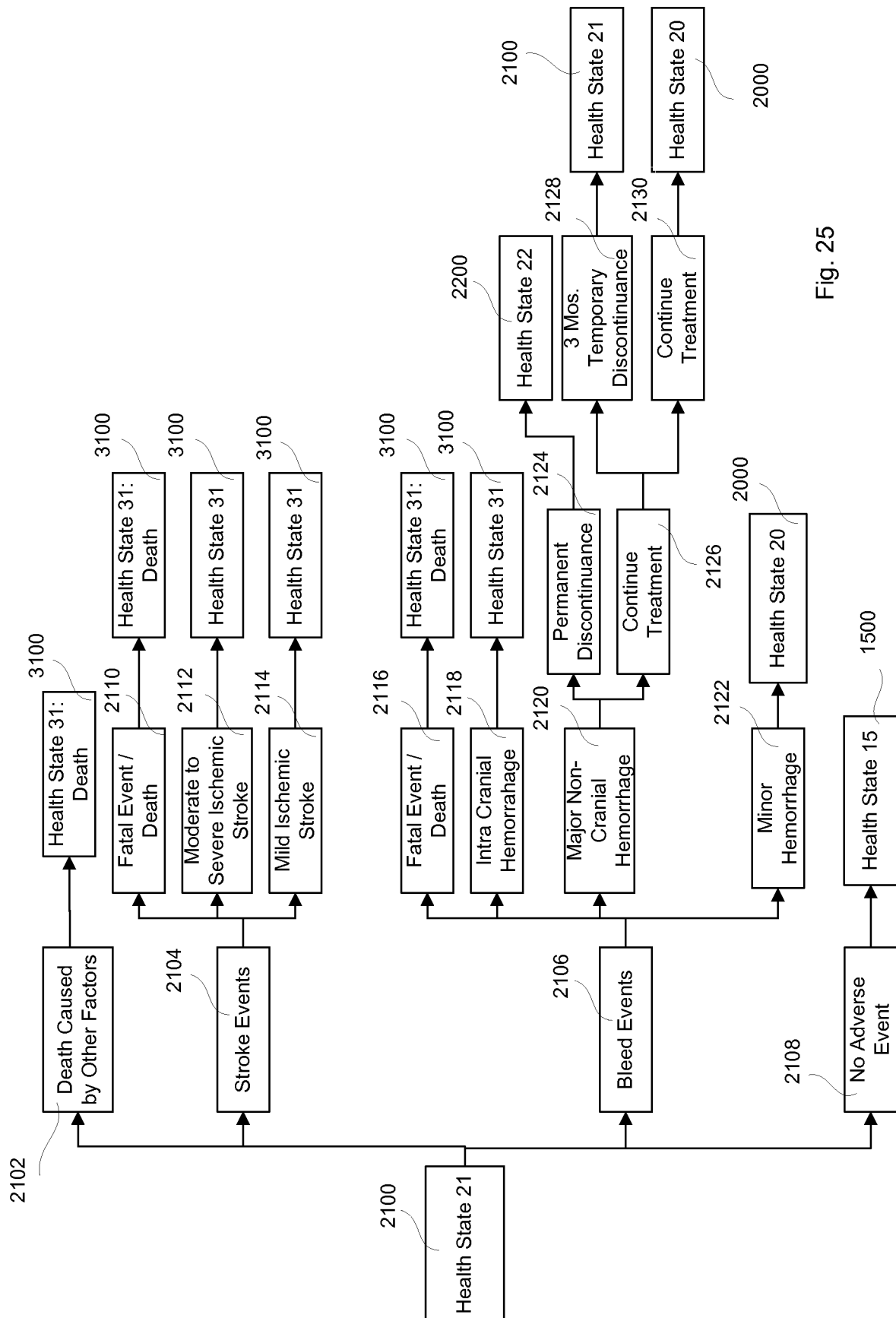


Fig. 25

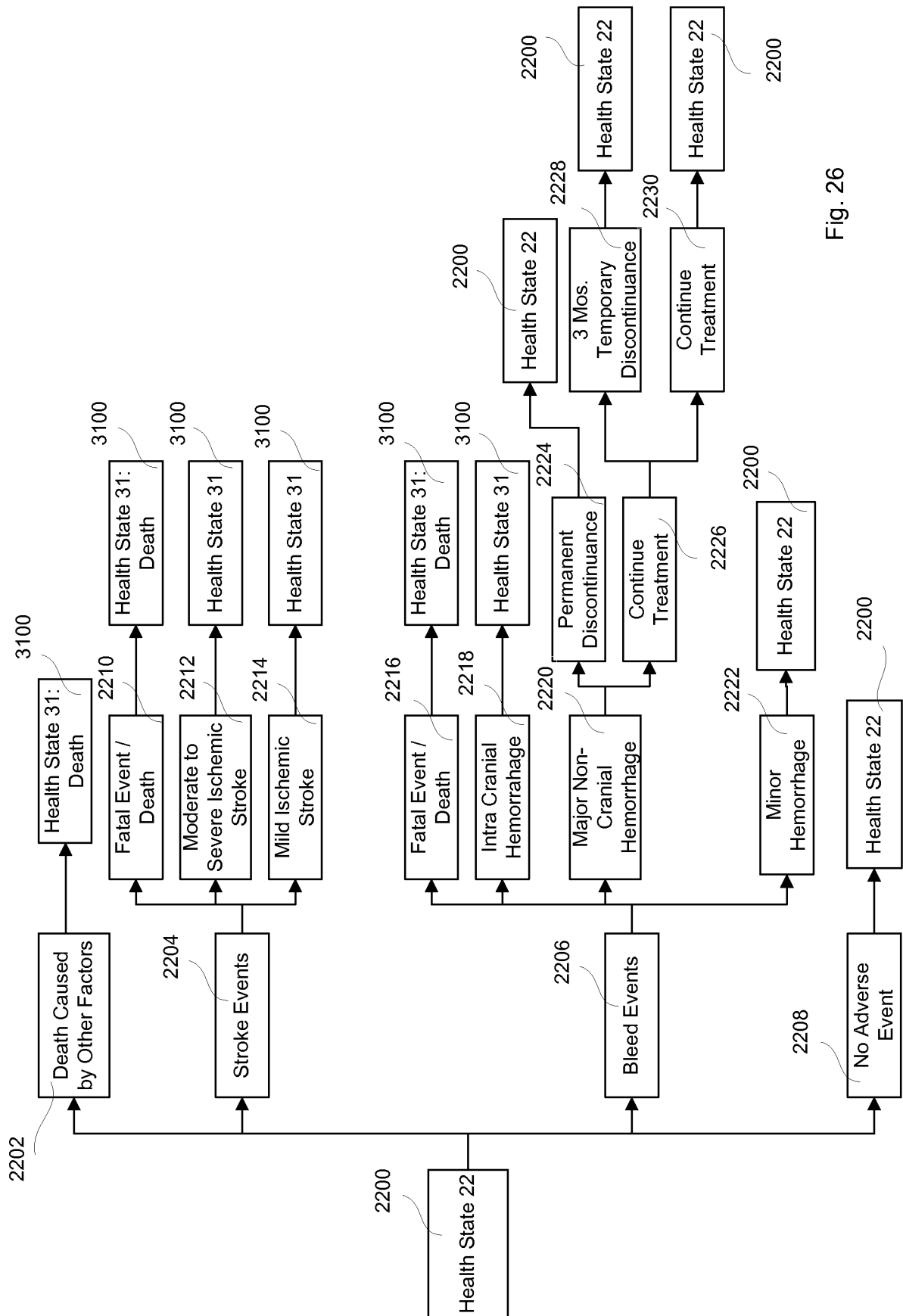


Fig. 26

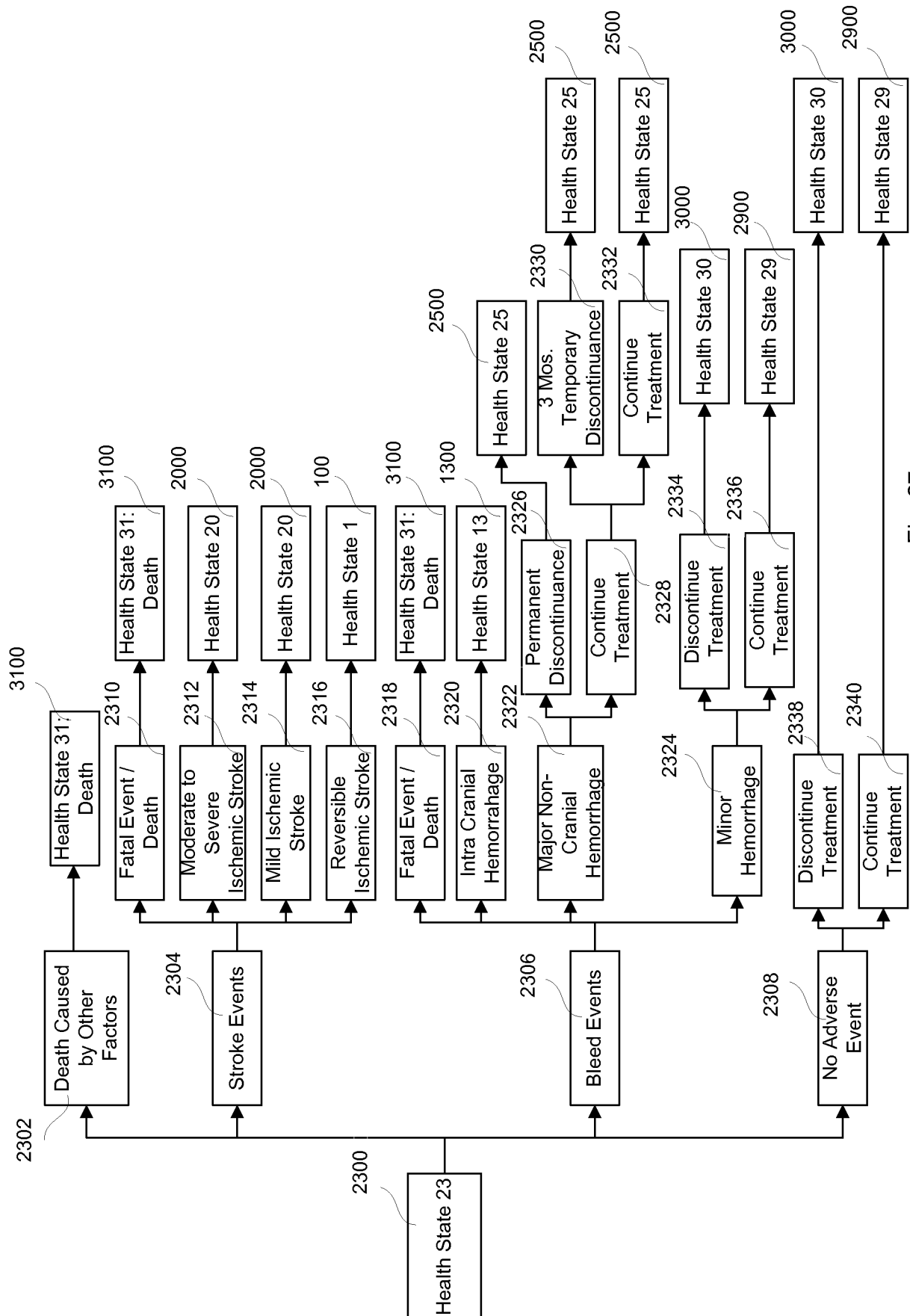


Fig. 27

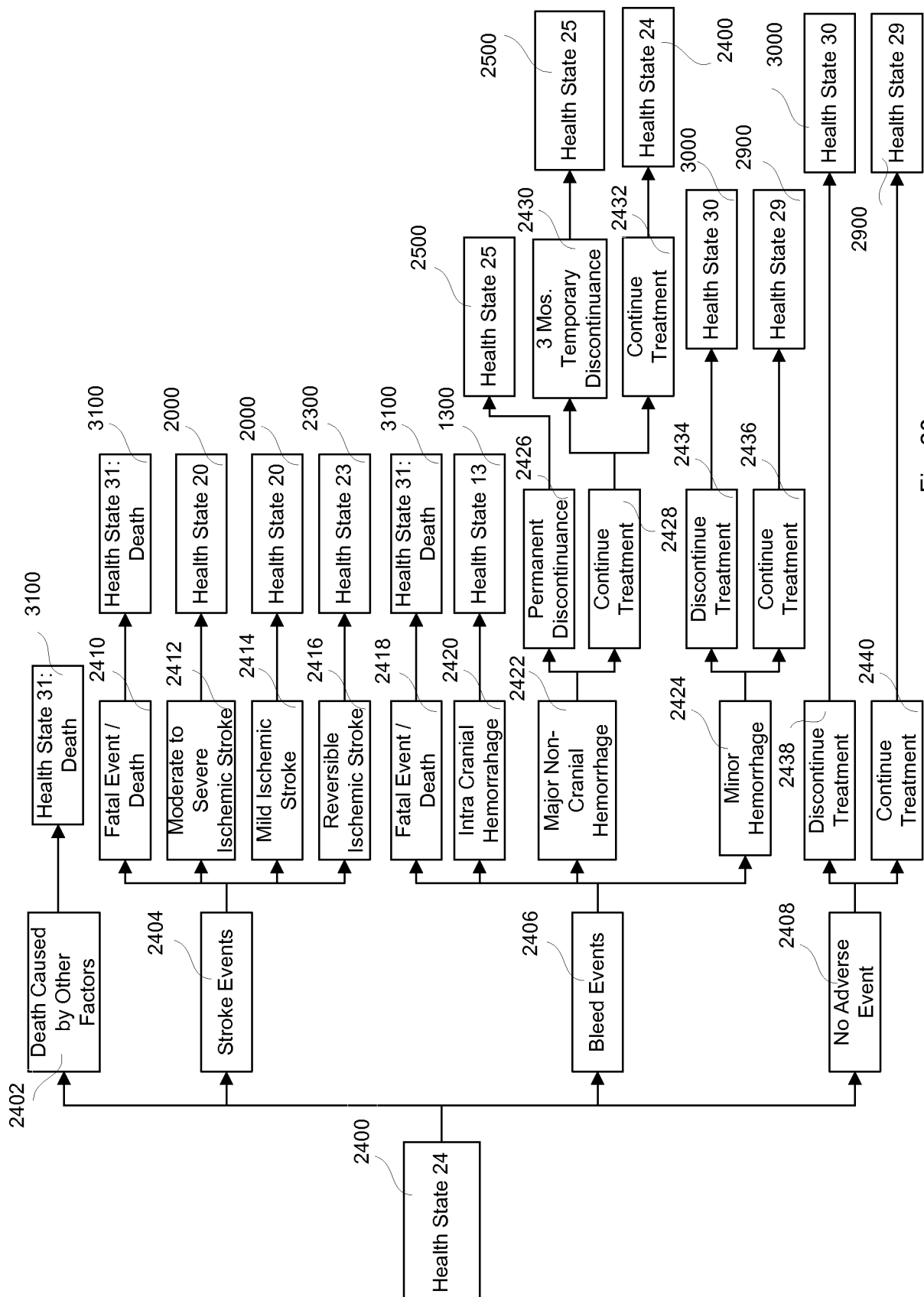


Fig. 28

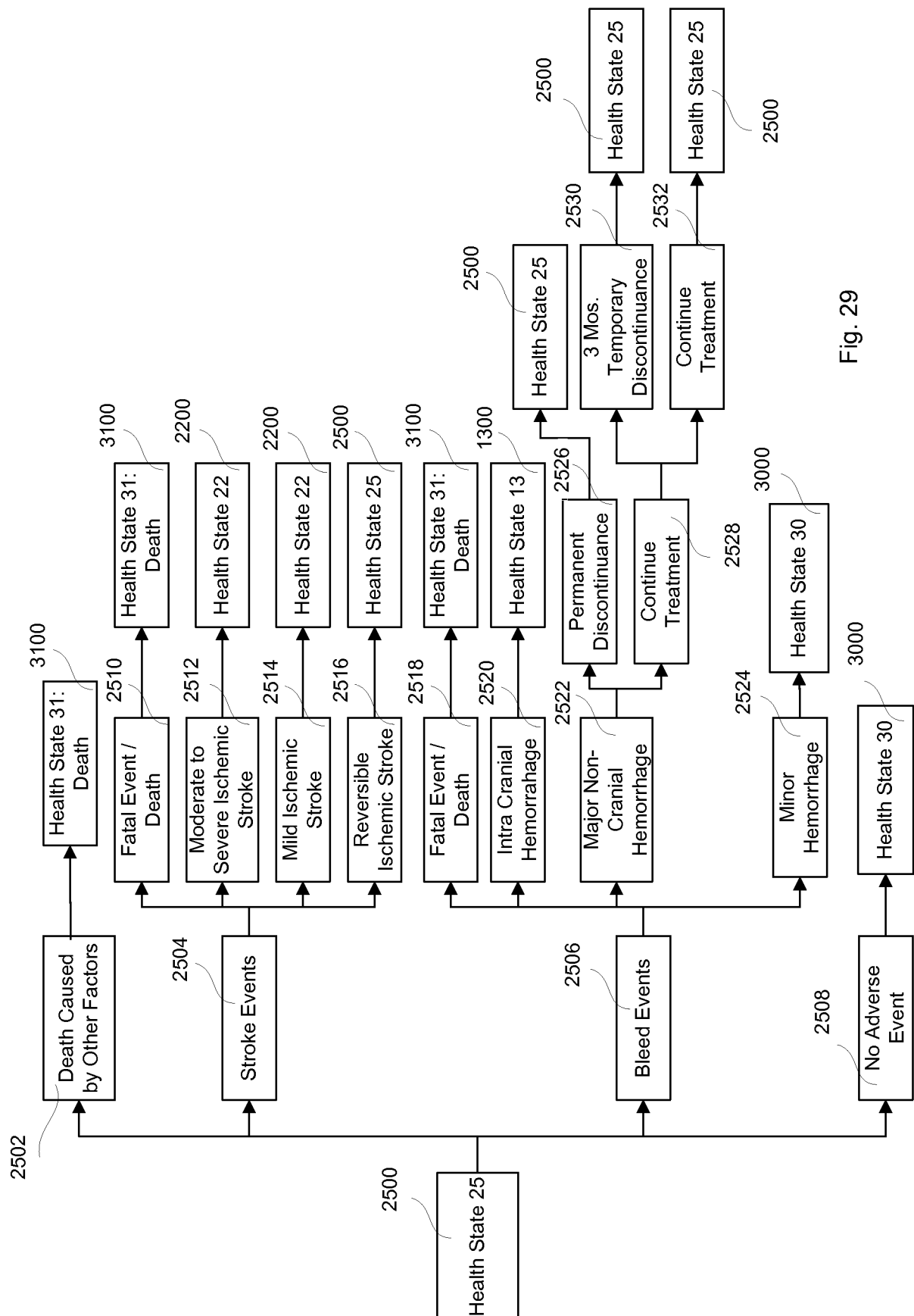


Fig. 29

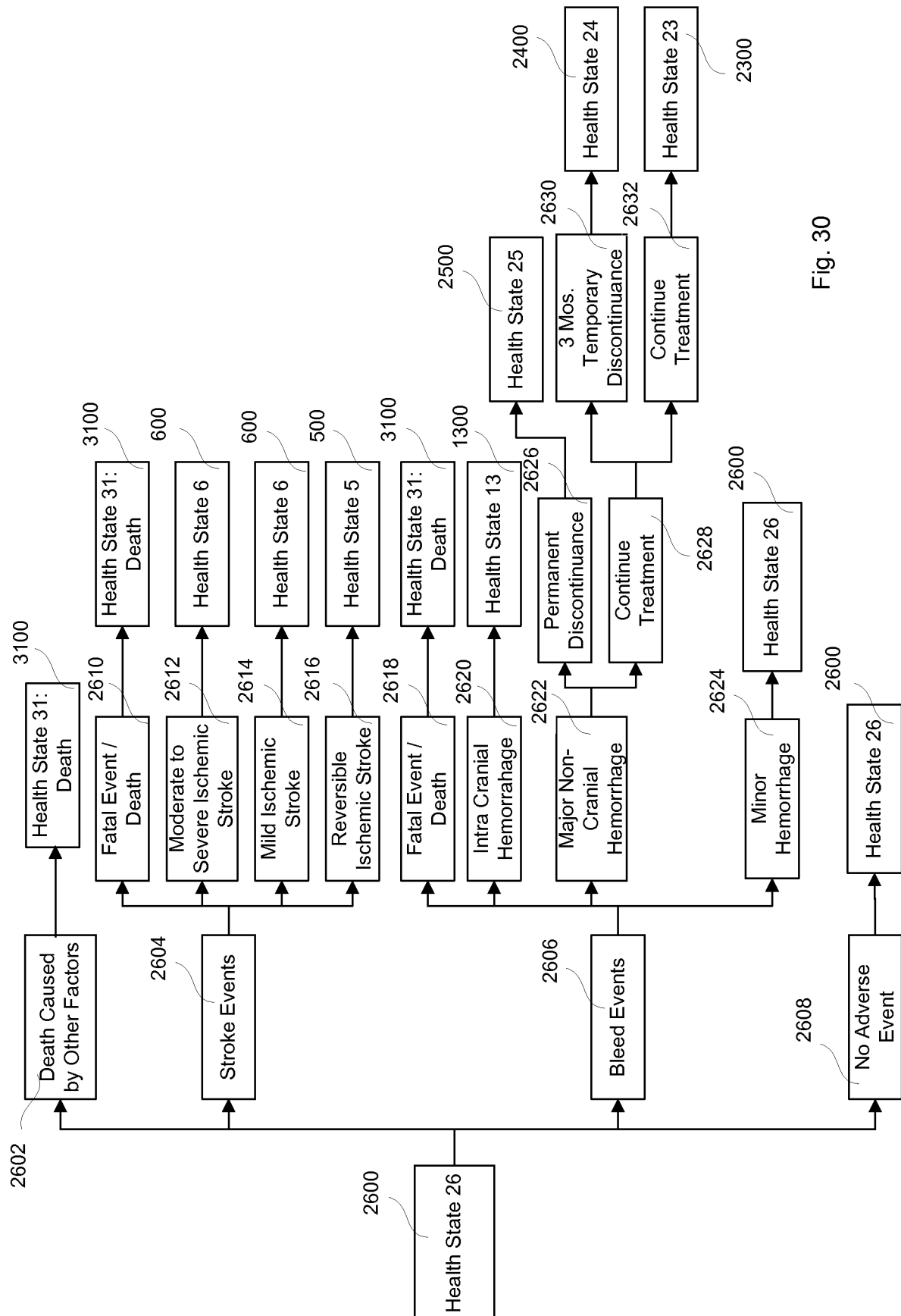


Fig. 30

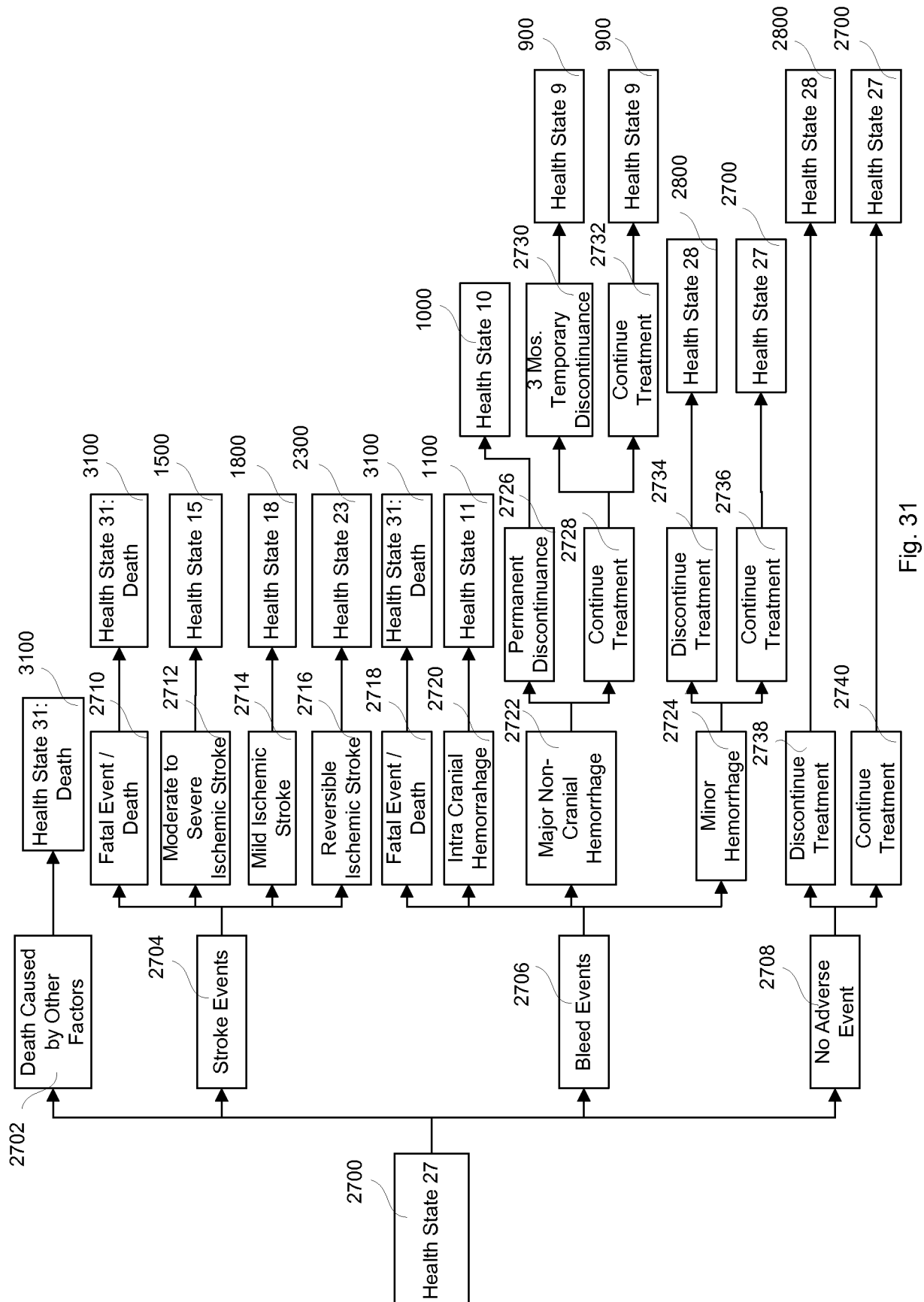


Fig. 31

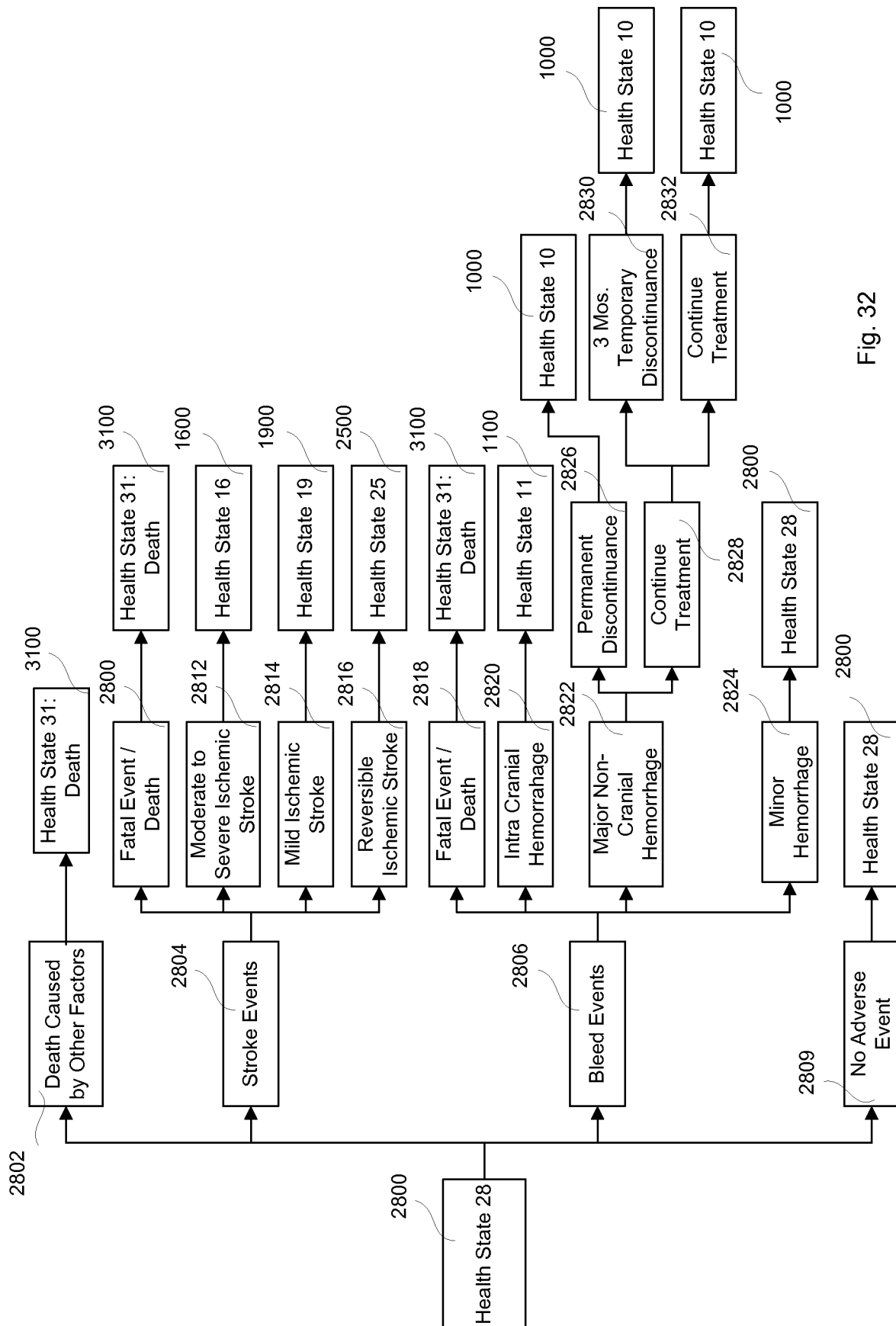


Fig. 32

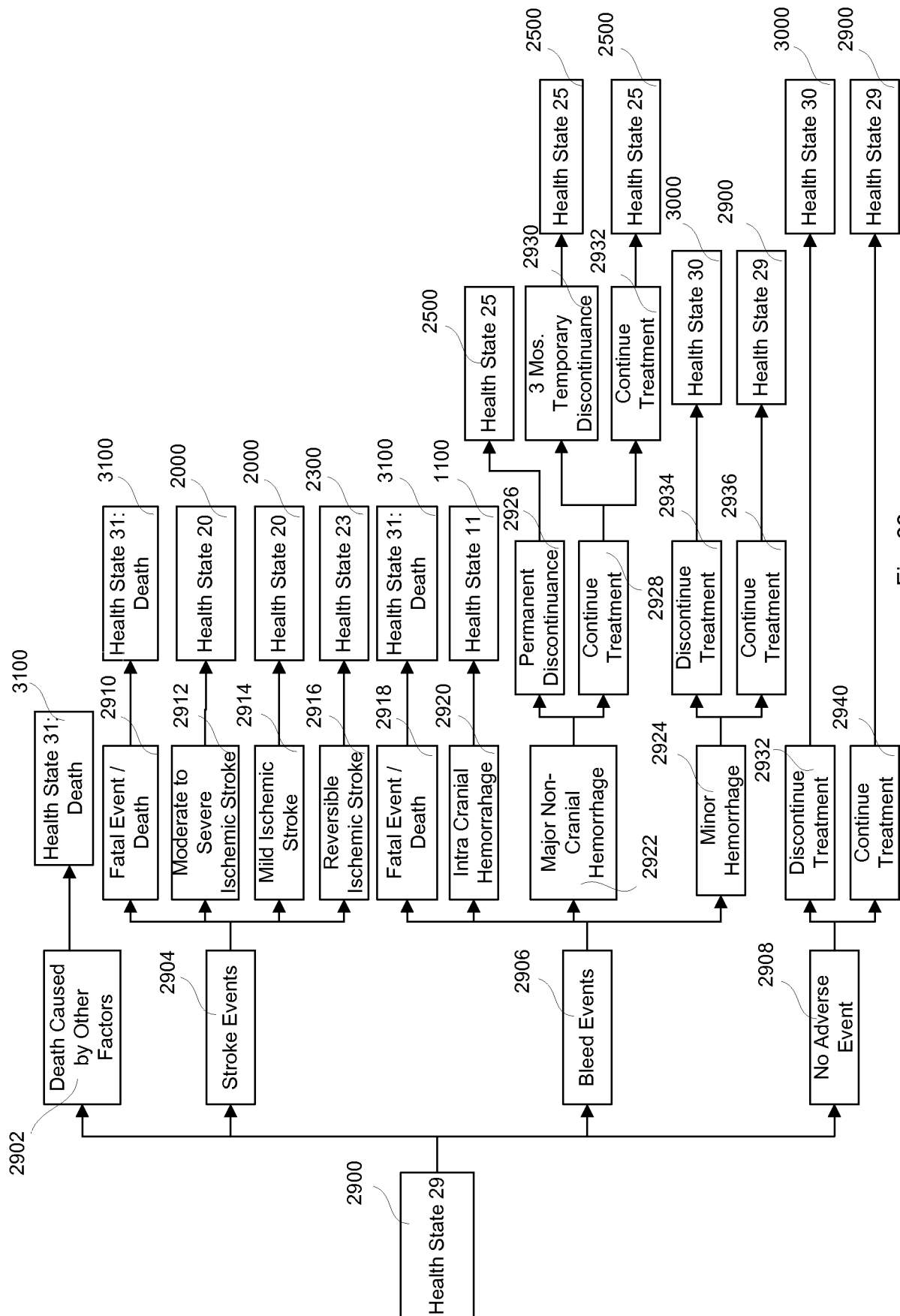


Fig. 33

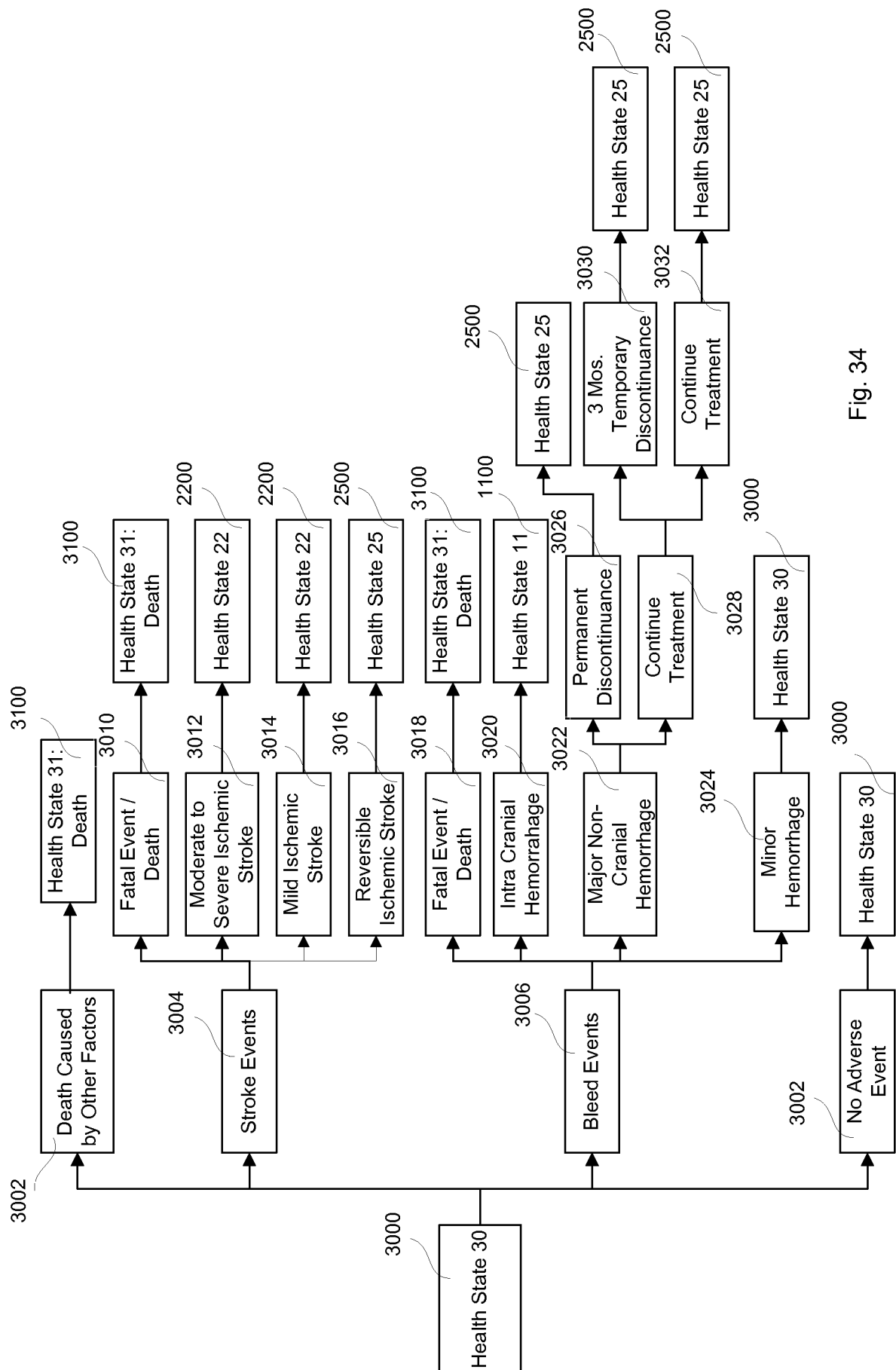


Fig. 34

Monte Carlo Simulation

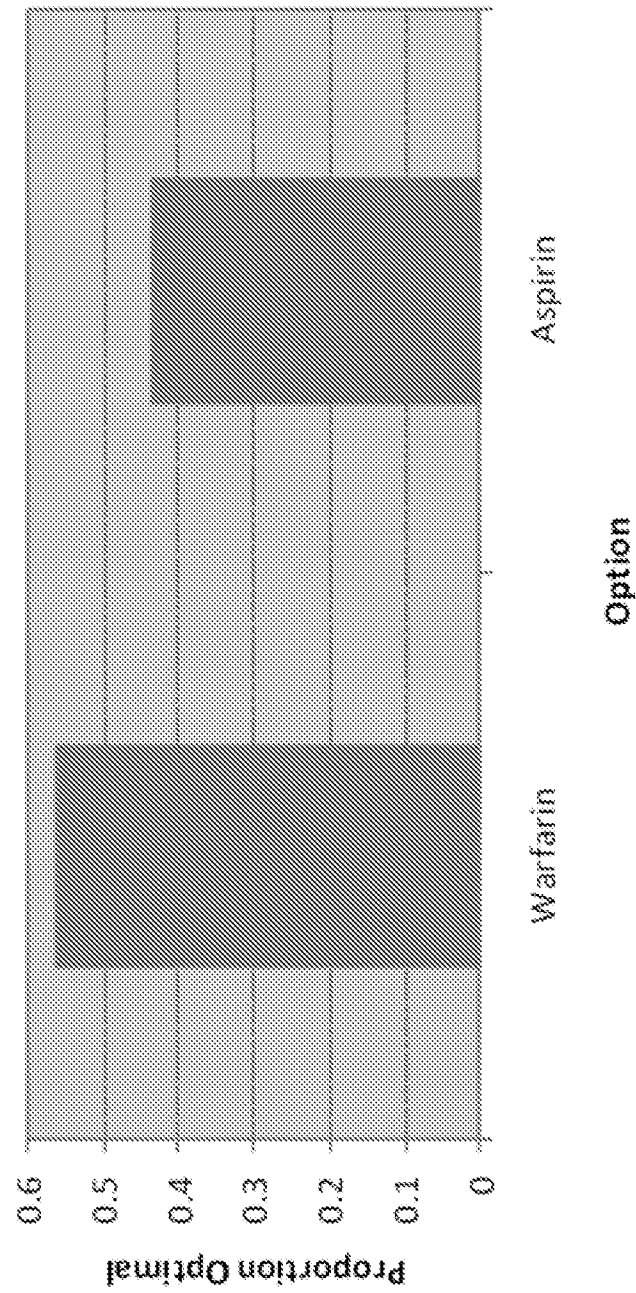


Fig. 35