Razvoj računalnoga programa za odabir terapijskog modaliteta u fibrilaciji atrija

Development of Software for Choosing Therapeutic Modalities in Atrial Fibrillation

Edin Begić[1]*,
Mensur Mandžuka[2],
Elnur Smajić[3],
Enisa Hodžić[4],
Amer Iglica[4],
Aida Mujaković[1],
Faris Zvizdić[4],
Amra Dobrača[5],
Azra Durak-Nalbantić[4]

[1]Opća bolnica "Prim. dr. Abdulah Nakaš", Sarajevo, Bosna i Hercegovina
[2]Netlight Consulting GmbH, München, Njemačka
[3]Univerzitski klinički centar Tuzla, Tuzla, Bosna i Hercegovina [4]Klinički centar Univerziteta u Sarajevu, Sarajevo, Bosna i Hercegovina
[5]Medicinski fakultet Univerziteta u Tuzli, Tuzla, Bosna i Hercegovina

[1]General Hospital «Prim. dr. Abdulah Nakaš», Sarajevo, Bosnia and Herzegovina
[2]Netlight Consulting GmbH, Munich, Germany
[3]University Clinical Center Tuzla, Tuzla, Bosnia and Herzegovina
[4]Clinical Center University of Sarajevo, Sarajevo, Bosnia and Herzegovina
[5]Faculty of Medicine, Tuzla, Bosnia and Herzegovina

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SAŽETAK: Fibrilacija atrija (FA) najčešća je tahiaritmija koja zahtijeva liječenje te je stalni klinički problem za liječnike obiteljske medicine i kardiologe. Razvijeno je nekoliko algoritama za procjenu rizika krvarenja u bolesnika s FA-om. Među njima su HAS-BLED (arterijska hipertenzija, abnormalna funkcija jetre i bubrega, moždani udar, anamnestički podatci ili predispozicija za krvarenje, labilna vrijednost INR-a, dob >65 godina, istodobno konzumiranje droge i alkohola), ORBIT (starija životna dob, snižena vrijednost hemoglobina/hematokrita/anemija, anamnestički podatci o krvarenju, snižena bubrežna funkcija, liječenje antitromboticima), ABC (životna dob, biomarkeri, anamnestički podatci), ATRIA (anemija, teško smanjenje bubrežne funkcije, dob >75 godina, prethodno krvarenje i dijagnosticirana arterijska hipertenzija) i HEMORR(2)HAGES (bolest jetre ili bubrega, alkoholizam, zloćudna bolest, starija životna dob, smanjen broj ili funkcija trombocita, ponovno krvarenje, arterijska hipertenzija, anemija, genski čimbenici, znatan rizik od pada i moždani udar). Primjena oralnih antikoagulanasa još je uvijek standard u prevenciji moždanog udara u FA, ali je treba uravnotežiti s rizikom od krvarenja koji je s njom povezan. Svrha je ovoga članka opisati razvoj sustava za podršku pri donošenju kliničkih odluka (CDSS; eng. *clinical decision support system*) koje bi liječnicima omogućile brzu procjenu rizika od krvarenja u bolesnika s FA-om kako bi optimizirali liječenje antikoagulansima. Spomenuti je računalni program razvijen u obliku mrežne aplikacije. Responzivni ustroj korisničkog sučelja bio je ključan u postizanju optimalne interakcije korisnika s programom te korisniku omogućuje potpunu kontrolu pri svakom koraku postupka neovisno o vrsti uređaja koja se primjenjuje, bilo to prijenosno računalo bilo pametni telefon. Pozadinski sustav aplikacije razvijen je u programskom jeziku *Python*. Preciznije rečeno, rabi se mrežni kostur zvan *Flask*. On se smatra dobrim izborom za brzo prototipiziranje, razvoj i uvođenje malih do srednjih aplikacija. Aplikacija razdvaja postupak odlučivanja u trima koracima. Prikaz prvog koraka traži od korisnika da izabere vrstu zbroja rizika koji želi izračunati. Sljedeći korak uključuje unošenje podataka o povijesti bolesti, laboratorijskim nalazima, simptomima i komorbiditetu. Posljednji ekran prikazuje izračunani zbroj rizika, koji pomaže korisniku u odabiru tijeka liječenja. Ovakav program nudi CDSS koji omogućuje bržu i lakšu procjenu rizika krvarenja u bolesnika s FA-om kako bi se postigao bolji terapijski modalitet. Responzivni ustroj i sučelje u obliku mrežne aplikacije osiguravaju lako pristupanje programu s pomoću širokog raspona uređaja.

SUMMARY: Atrial fibrillation (AF) is the most common tachyarrhythmia that requires treatment and represents constant clinical problem for general practitioners and cardiologists. Several bleeding risk scores have been developed for estimating bleeding risk in patients with AF. These include: HAS-BLED (hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, age >65 years, drugs/alcohol concomitantly), ORBIT (older age, reduced hemoglobin/hematocrit/anemia, bleeding history, insufficient kidney function, treatment with antiplatelets), ABC (age, biomarkers, clinical history), ATRIA (anemia, severe renal disease, age ≥75 years, previous hemorrhage, and diagnosed hypertension), and HEMORR(2)HAGES (Hepatic or Renal Disease, Ethanol Abuse, Malignancy, Older Age, Reduced Platelet Count or Function, Re-Bleeding, Hypertension, Anemia, Genetic Factors, Excessive Fall Risk, and Stroke). The use of oral anticoagulants is still the standard in stroke prevention in AF but should be balanced against the associated bleeding risk. The aim of this article was to describe the development of a clinical decision support system (CDSS) that will enable clinicians to perform a quick assessment of bleeding risk in patients with AF in order to optimize anticoagulation therapy in patients with AF. The software was developed in the form of a web application. The responsive design of the interface was key to optimal user interaction, providing seamless control of every step of the process regardless of the type of device used, whether a laptop or a smartphone. The backend of the application was developed in Python. More specifically, a web framework named Flask was utilized. It is considered to be a good choice for rapid prototyping and development and deployment of small- to medium-sized applications. The application separates the decision process into three steps. Displaying the first step prompts the user to select the type of score they want calculated. The following step includes entering anamnestic data, laboratory findings, symptoms, and comorbidities. The final screen displays the calculated score, which assists the user in determining the course of the treatment. This software represents a CDSS that enables faster and easier assessment of bleeding risk in patients with AF in order to achieve a better therapeutic modality. The responsive design and the web application format makes the software easily accessible on a wide range of devices.

KLJUČNE RIJEČI: fibrilacija atrija, sustav za podršku pri donošenju kliničkih odluka, antikoagulantno liječenje, rizik, krvarenje.

KEYWORDS: atrial fibrillation, clinical decision support system, anticoagulants, risk, bleeding.

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***ADDRESS FOR CORRESPONDENCE**: Edin Begić, General Hospital «Prim.dr.Abdulah Nakas», Kranjčevićeva 12, 71000 Sarajevo, Bosnia and Herzegovina. / Phone: +387-61-303375 / E-mail: edinbegic90@gmail.com

ORCID: Edin Begić, https://orcid.org/0000-0001-6842-262X • Mensur Mandžuka, https://orcid.org/0000-0002-8102-2783
Elnur Smajić, https://orcid.org/0000-0003-0881-9443 • Enisa Hodžić, http://www.orcid.org/0000-0002-7436-7708
Amer Iglica, https://orcid.org/0000-0002-4677-8489 • Aida Mujaković, https://orcid.org/0000-0002-0022-1482
Faris Zvizdić, https://orcid.org/0000-0001-7647-2723 • Amra Dobrača, https://orcid.org/0000-0002-1996-9714
Azra Durak-Nalbantić, https://orcid.org/0000-0002-5175-8941

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Liječenje fibrilacije atrija

Fibrilacija atrija (FA) najčešća je tahiaritmija koja zahtijeva liječenje te je stalni klinički problem za liječnike obiteljske medicine i kardiologe.[1] Elektrofiziološki gledano, FA nastaje zbog kružnoga kretanja električnih impulsa na nekoliko mjesta u atriju, ali se, za razliku od klasičnog fenomena ponovnog ulaska, impulsi kreću nepravilno i neravnomjerno te depolariziraju atrije, u nastavku cirkulirajući na miofibrilima atrija, pa je električna aktivnost atrija potpuno dezorganizirana i nije popraćena kontrakcijom atrija. Intrakardijalni elektrofiziološki pregled jasno pokazuje postojanje promijenjenoga tkiva u atriju, tj. postojanje patoanatomskog supstrata, koji pokreće i djelomično održava FA.[1] Klasifikacija se provodi na temelju ventrikulskog odgovora na elektrokardiogramu.[2] Ako je frekvencija klijetki 60 – 100 u minuti, postavlja se dijagnoza FA ili apsolutne aritmije; frekvencija <60/min dijagnosticira se kao apsolutna bradiaritmija; frekvencija >100/min dijagnosticira se kao apsolutna tahiaritmija; u slučaju QRS-kompleksa sa sporom frekvencijom i regularnim intervalima dijagnosticira se FA s totalnim srčanim blokom.[2,3] Postoji nekoliko vrsta koje razlikujemo na temelju pojavljivanja, trajanja i spontanog prestanka epizode FA: paroksimalna, perzistentna, dugotrajna perzistentna i trajna FA.[3]

Incidencija FA-a je 0,4 % u osoba do 60 godina, 2,0 – 5,0 % u onih starijih od 60 i 12,0 % u onih nakon 75. godine. Češća je u muškaraca.[3,4] Oko 4 % kardioloških bolesnika i oko 40 % osoba s kongestivnim zatajivanjem srca ima FA.[4]

Nedostatak kontrakcije atrija i izmijenjena i proširena lijeva klijetka uzrokuje stvaranje ugrušaka. Liječenje FA-a temelji se prije svega na uklanjanju simptoma ili postizanju sinusnog ritma u perzistentnoj FA ili regulaciji frekvencije klijetki u permanentnom FA-u, uz prevenciju tromboembolijskih komplikacija.[2,3] U permanentnom se FA-u, uz antiaritmike, liječenje temelji na antikoagulantnim lijekovima kako bi se prevenirali tromboembolijski događaji.[3,4]

Najčešće primjenjivani oralni antikoagulantni lijekovi derivati su kumarina, od kojih se najčešće rabi varfarin.[5] Ti se lijekovi (varfarin, etilbiskumacetat, acenokumarol, fenprokumon) razlikuju u pouzdanosti, farmakološkim obilježjima (stupanj i opseg apsorpcije) i trajanju učinka.[5,6] Vežu se za albumin, metaboliziraju hidroksilacijom u jetri i izlučuju urinom.[6] Oralni antikoagulantni lijekovi djeluju samo *in vivo* te

Management of atrial fibrillation

Atrial fibrillation (AF) is the most common tachyarrhythmia that requires treatment and presents an almost ubiquitous clinical problem for general practitioners and cardiologists.[1] Electrophysiologically, AF occurs due to the circular movement of electrical impulse at several sites in the atria, but, unlike the classic reentry phenomenon, the impulses move irregularly and unequally and depolarize the atria, subsequently circulating on the myofibrils of the atria, so the electrical activity of the atria is completely disorganized and not accompanied by contraction of the atrium. Intracardial electrophysiological examination clearly indicates the existence of altered tissue in the atria, i.e. of a pathoanatomic substrate, which initiates and partially maintains AF.[1] The classification is made according to ventricular response on an electrocardiogram.[2] If the ventricular response frequency is 60-100 per minute, AF or absolute arrhythmia is diagnosed; a frequency is below 60 per minute is diagnosed as absolute bradyarrhythmia; ventricular frequency over 100 per minute is diagnosed as absolute tachyarrhythmia; and AF with complete heart block is diagnosed in case of QRS complexes with a slow rate and regular interval.[2,3] There are several types of AF based on the presentation, duration, and spontaneous termination of an AF episode: paroxysmal, persistent, long-standing persistent, and permanent AF.[3]

Incidence of AF is 0.4% in adults up to 60 years of age, in 2.0-5.0% in people who are older than 60 years, and 12.0% in patients over 75 years. It is more likely to occur in men.[3,4] About 4% of cardiac patients and about 40% of those with congestive heart failure have AF.[4]

Lack of atrial contraction and an altered and dilated left ventricle result in thrombus formation. Treatment of AF is primarily based on elimination of symptoms or achievement of sinus rhythm in persistent AF or regulation of the ventricular frequency in permanent AF, as well as the prevention of thromboembolic diseases.[2,3] In permanent therapy, in addition to antiarrhythmic drugs, anticoagulant drugs are the basis of therapy due to the prevention of thromboembolic incidents.[3,4]

The most commonly used oral anticoagulants are coumarin derivatives, of which warfarin is the most commonly used.[5] They (warfarin, ethylbiscumacetate, acenocoumarol,

nemaju nikakav učinak na zgrušavanje ako se krvi dodaju *in vitro*.[5,6] Zahvaljujući strukturalnoj sličnosti vitaminu K, oralni antikoagulansi kompetitivno inhibiraju enzimsku redukciju vitamina K u njegov aktivni hidrokinonski oblik.[7] Varfarinski se učinak prati mjerenjem protrombinskoga vremena (PV), čija se vrijednost izražava kao INR (eng. *international normalized ratio*). Razne bolesti te primjena mnogih lijekova može potencirati učinak varfarina, čime se povećava rizik od krvarenja.[7]

Bolest jetre može utjecati na sintezu koagulacijskih čimbenika. Postoje i uvjeti u kojima povišene razine metaboličkih procesa (a time i degradacija koagulacijskih čimbenika), kao što su visoka temperatura ili tireotoksikoza, također mogu pojačati učinak antikoagulacijskih lijekova. Mnogi lijekovi mogu potencijalno pojačati učinke varfarina.[6-8] To uključuje lijekove koji inhibiraju metabolizam u jetri, primjerice: cimetidin, imipramin, kotrimoksazol, kloramfenikol, ciprofloksacin, metronidazol, amiodaron i različiti lijekovi iz azolske skupine antimikotika.[8] Nesteroidni protuupalni lijekovi (NSAID; eng. *non-steroidal anti-inflammatory drugs*) i neki antibiotici (moksalaktam i karbenicilin) također utječu na funkciju trombocita.[7,8] Acetilsalicilatna kiselina povećava rizik od krvarenja ako se daje bolesnicima koji se liječe varfarinom, iako je primjena te kombinacije sigurna uz pažljivo praćenje.[7] Lijekovi koji premještaju varfarin s mjesta vezanja u albuminu u plazmi, kao što su neki od NSAID-ova ili kloralhidrat, uzrokuju prolazno povećanje koncentracija varfarina izvan plazme.[7,8] Lijekovi koji inhibiraju smanjenje vitamina K, kao što su cefalosporini, mogu utjecati na učinke varfarina.[8]

Svi bolesnici s vrijednostima na zbroju rizika CHA_2DS_2VASc (koji se rabi za procjenu rizika od tromboembolijskog događaja) ≥1 trebaju biti liječeni oralnim antikoagulancijama ako ne postoje kontraindikacije.[2,9] Primjena antikoagulantnih lijekova zahtijeva multidisciplinarni pristup i procjenu rizika od krvarenja. Sama procjena rizika pak zahtijeva dobre anamnestičke podatke i detaljnu dijagnostičku obradu. Trenutačno se u kliničkoj praksi uporabljuje pet novih antikoagulancija (NOAC; eng. *new oral anticoagulants*) za prevenciju moždanog udara u pacijenata s FA-om ili za prevenciju duboke venske tromboze. Ti lijekovi uključuju dabigatran (izravni inhibitor trombina) i inhibitore čimbenika Xa – rivaroksaban, betriaksaban, apiksaban i edoksaban. Prednosti NOAC-a uključuju predvidljivu farmakokinetiku.[9]

Pri uporabi NOAC-a nema potrebe za praćenjem terapije i prilagođivanjem doze kao kod varfarina. Klinička ispitivanja na učincima NOAC-a pokazala su da su jednako učinkoviti kao varfarin u prevenciji moždanog udara ili sustavne embolije.[3,9] Stoga najnovije Smjernice Europskog kardiološkog društva za FA preporučuju primjenu NOAC-a u novih bolesnika. Mogući nedostatci NOAC-a uključuju rizik od krvarenja koji je povećan u osoba starijih od 75 godina, povećanu učestalost gastrointestinalnog krvarenja kod primjene visokih doza dabigatrana, povećanu učestalost dispepsije kod primjene dabigatrana, nedostatak rutinskih laboratorijskih testova koji bi pouzdano mjerili antikoagulacijski učinak i nedostatak protulijeka koji se uporabljuje u svakodnevnoj kliničkoj praksi.[3,9] Izravne usporedbe NOAC-a u randomiziranim kliničkim ispitivanjima nisu provedene, a izbor NOAC-a ovisi o kliničkom stanju i komorbiditetima.[9]

Iako se preporučuje uporaba NOAC-a, i dalje primjena antagonista vitamina K ili varfarina nije zabranjena. Terapijski modalitet pacijenata s FA-om zahtijeva procjenu rizika od krvarenja. Krvarenje je potencijalno najopasnija nuspojava antikoagulacij-

phenprocoumon) differ in reliability, pharmacological characteristics (degree and extent of absorption) and duration of effect.[5,6] They bind to albumin, metabolize with hydroxylation in the liver, and are excreted in the urine.[6] Oral anticoagulant drugs only act *in vivo* and have no effect on clotting if are added to blood *in vitro*.[5,6] Thanks to their structural similarity with vitamin K, oral anticoagulants competitively inhibit the enzymatic reduction of vitamin K to its active hydroquinone form.[7] The warfarin effect is monitored by measuring prothrombin time (PT), the values of which are expressed as the International Normalized Ratio (INR). Various diseases, and also the use of many drugs, can potentiate the effect of warfarin, thus increasing the risk of hemorrhages.[7]

Liver disease can influence the synthesis of coagulation factors. Furthermore, there are conditions where elevated levels of metabolic processes (and therefore degradation of coagulation factors), such as high temperature or thyrotoxicosis, can also increase the effect of anticoagulant drugs. Many drugs can potentially intensify the effects of warfarin.[6-8] This includes agents that inhibit drug metabolism in the liver, for example: cimetidine, imipramine, cotrimoxazole, chloramphenicol, ciprofloxacin, metronidazole, amiodarone, and various drugs from the azole group of antimycotics.[8] Nonsteroidal anti-inflammatory drugs (NSAIDs) and some antibiotics (moxalactam and carbenicillin) also alter the platelet function.[7,8] Aspirin increases the risk of bleeding if given to patients who are on warfarin therapy, although this combination can be safely used if carefully monitored.[7] Drugs that displace the warfarin from the binding site in plasma albumin, such as some of the NSAIDs or chloral hydrate, lead to a transitory increase in plasma-free warfarin concentrations.[7,8] Drugs that inhibit vitamin K reduction, such as cephalosporins, may affect the effects of warfarin.[8]

All patients with AF and a CHA_2DS_2VASc score (used to assess the risk of thromboembolic incident) of 1 or over must receive oral anticoagulant therapy if there are no contraindications.[2,9] However, the use of anticoagulants requires a multidisciplinary approach and assessment of the bleeding risk as a consequence of anticoagulant therapy. The risk assessment itself requires quality anamnestic data and detailed diagnostic treatment of the patient. Five new oral anticoagulants (NOAC) are currently used in clinical practice (for prevention of stroke in patients with AF or for the prevention of deep vein thrombosis). These include the direct thrombin inhibitor, dabigatran, and factor Xa inhibitors rivaroxaban, betriaxaban, apixaban, and edoxaban. The benefits of NOAC include predictable pharmacokinetics.[9]

There is no need for therapeutic monitoring and dose adjustments, as in the case of warfarin derivatives. Clinical trials on the effects of NOAC proved them to be as effective as warfarin in the prevention of stroke or systemic embolism.[3,9] Consequently, the latest guidelines of the European Society of Cardiology on AF recommended the use of NOAC in new patients. Potential deficiencies of NOAC include the risk of bleeding that can be increased in patients over 75 years of age, increased gastrointestinal hemorrhage with high doses of dabigatran, increased dabigatran dyspepsia, lack of routine laboratory tests to reliably measure the anticoagulant effect, and lack of antidotes used in everyday clinical practice.[3,9] No direct comparisons of NOACs in randomized controlled trials were conducted, and the choice of NOAC depends on the patient's co-morbidity but also on their clinical status.[9]

skih lijekova (pogotovo u crijevima ili u mozgu).[3] Ovisno o hitnosti situacije, liječenje posljedičnoga krvarenja može biti u rasponu od privremenog prekida varfarina (u slučaju manjega krvarenja) do primjene vitamina K, svježe plazme ili koncentrata koagulacijskih čimbenika (pri krvarenjima koja su opasna za život).[8]

Razvijeno je nekoliko algoritama za procjenu rizika od krvarenja u pacijenata s FA-om. Među njima su HAS-BLED (arterijska hipertenzija, abnormalna funkcija jetre i bubrega, moždani udar, anamnestički podatci ili predispozicija za krvarenje, labilna vrijednost INR-a, dob >65 godina, istodobno konzumiranje droge i alkohola), ORBIT (starija životna dob, snižena vrijednost hemoglobina/hematokrita/anemija, anamnestički podatci o krvarenju, snižena funkcija bubrega, liječenje antitromboticima), ABC (životna dob, biomarkeri, anamnestički podatci), ATRIA (anemija, teško smanjenje bubrežne funkcije, dob >75 godina, prethodno krvarenje i dijagnosticirana arterijska hipertenzija) i HEMORR(2)HAGES (bolest jetre ili bubrega, alkoholizam, zloćudna bolest, starija životna dob, smanjen broj ili funkcija trombocita, ponovno krvarenje, arterijska hipertenzija, anemija, genski čimbenici, značajan rizik od pada i moždani udar).[3,10-12] Primjena oralnih antikoagulancija još je uvijek standard u prevenciji moždanog udara u FA-u, ali je treba uravnotežiti s povezanim rizikom od krvarenja.[10,12]

Sustav za podršku pri donošenju kliničkih odluka

Informatičke tehnologije mogu imati velik utjecaj na kliničku praksu u smislu razvoja sustava za podršku pri donošenju kliničkih odluka, koji uključuju sve vrste sustava čija je primarna funkcija preuzimanje podataka koji se mogu primijeniti u postupku odlučivanja. To su interaktivni računalni sustavi zasnovani na podatcima i modelima koji pomažu u rješavanju problema i donošenju odluka. U medicini su takvi sustavi alati koji sadržavaju utvrđeno kliničko znanje i podatke vezane za bolesnika u svrhu poboljšanja skrbi. Svrha im je da pomažu pri interakciji između bolesnika i liječnika od trenutka prvog posjeta, tijekom cijeloga dijagnostičkog postupka te u razdoblju praćenja. Vremenska ograničenja koja su posljedica stalnog razvoja u standardu liječenja pridonose broju medicinskih pogrešaka i kašnjenja u kliničkim odlukama.[13,14]

Uporaba sustava za podršku pri donošenju odluka široko je rasprostranjena u svim stručnim djelatnostima, a takvi sustavi, koji pomažu pri donošenju oduka u medicinske i zdravstvene svrhe, nazivaju se sustavima za podršku pri donošenju kliničkih odluka (CDSS; eng. *clinical decision support system*).[13] Zbog raspoloživosti računalne opreme i programa u obliku mobilnih sustava za podršku pri donošenju kliničkih odluka njihova primjena postaje sve češća u modernoj medicini. Takvi se sustavi uporabljuju na mobilnim uređajima, gdje ih je moguće nabaviti preko službene aplikacijske trgovine za tu vrstu uređaja. Moderni mobilni uređaji mogu provoditi složene kalkulacije i uvijek su na raspolaganju.

Pojedini CDSS-i razlikuju se po vrsti i složenosti. Sustav može biti pasivan (korisnik mora izričito poslati zahtjev za podršku), poluaktivan (promatrački sustavi koji rade automatski, no iznose podatke samo na zahtjev korisnika) i aktivan (automatski se aktiviraju, iznose podatke bez čekanja na zahtjev, a katkad i donose odluku bez interakcije sa zdravstvenim djelatnikom).[14] Takvi se sustavi uvode kako bi se pružila podrška zdravstvenim djelatnicima širokog raspona specijalizacija na način koji može biti prilagođen za različite razine stručnog znanja.

Although the use of NOAC is recommended, the use of vitamin K antagonists or warfarin derivatives is not disallowed. The therapeutic modality of patients with AF requires an assessment of the risk of bleeding. Bleeding is potentially the most dangerous side-effect of anticoagulant drugs (especially in the intestine or brain).[3] Depending on the urgency of the situation, the treatment of the resulting hemorrhage ranges from the interruption of the use of warfarin (in case of minor bleeding) to administration of vitamin K, fresh plasma, or coagulation factor concentrates (for life-threatening bleedings).[8]

Several bleeding risk scores have been developed for estimating bleeding risk in patients with AF. These include: HAS-BLED (hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile INR, elderly (>65 years), drugs/alcohol concomitantly), ORBIT (older age, reduced hemoglobin/ hematocrit/anemia, bleeding history, insufficient kidney function, treatment with anti-platelets), ABC (age, biomarkers, clinical history), ATRIA (anemia, severe renal disease, age ≥75 years, previous hemorrhage, and diagnosed hypertension), and HEMORR(2)HAGES (Hepatic or Renal Disease, Ethanol Abuse, Malignancy, Older Age, Reduced Platelet Count or Function, Re-Bleeding, Hypertension, Anemia, Genetic Factors, Excessive Fall Risk, and Stroke).[3,10-12] The use of oral anticoagulants is still the standard in stroke prevention in AF but should be balanced against associated bleeding risk.[10,12]

The clinical decision support system

Information technologies can have a big impact on medical practice in terms of developing decision support systems, which include all types of systems whose primary function is to take the information that can be used in the decision-making process. These are interactive, computer-based systems based on data and models that help solve problems and make decisions. Decision-making support systems in medicine are tools that contain established clinical knowledge and patient-oriented information to improve patient care. Their purpose is to assist in interaction between the patient and the physician from the moment of initial consultation, throughout the diagnostic process, and in the follow-up period. Time constraints caused by constant evolution of the standard of care contribute to the number of medical mistakes and delays in clinical decisions.[13,14]

The use of decision support systems is widespread in all aspects of professional activity, and such systems that support decision-making for medical and healthcare purpose are called clinical decision support systems (CDSSs).[13] Due to the availability of hardware and availability of software in form of Mobile Clinical Decision Support Systems, their use in modern medicine is becoming more and more frequent. These systems are used on mobile devices and can be obtained via the official app store for the particular platform. Modern mobile devices can perform complex calculations and are available at all times.

CDSSs vary by type and complexity. The systems can be passive (the user explicitly sends the support request), semi-active (observation systems that are automatically executed but present information only at user request), and active (automatically activated, present information without waiting on request, and sometimes make a decision without interaction with a healthcare professional).[14] These systems are implemented to support healthcare professionals within a broad spectrum of specialization and tailored to different levels of expert knowledge.

Najjednostavniji primjer CDSS-a provjerava podatke koje unosi zdravstveni djelatnik i traži vrijednosti u referentnom rasponu. Krajnji je rezultat određena vrsta obavijesti ili podsjetnika. CDSS-i srednje složenosti uključuju prognostičke kalkulatore i automatske smjernice u kliničkoj praksi. Prognostički se kalkulatori rabe za automatsko predviđanje, najčešće na osnovi kliničkih bodovnih sustava. Složeni CDSS-i koriste se umjetnom inteligencijom, dubinskom analizom podataka ili statističkim metodama kako bi svrstali i predvidjeli bolest ili stanje pacijenta.[14]

Ovakve metode automatski određuju ključna svojstva koja su važna za kliničku klasifikaciju ili predviđanje problema te se koriste matematičkim alatima kako bi odredile način na koji ta obilježja treba kombinirati u svrhu izvođenja neke klasifikacije ili predviđanja.

CDSS-e se može svrstati u šest kategorija: podrška pri određivanju doze lijekova, pomoć pri naručivanju, podsjetnici/upozorenja na mjestu liječenja, prikazivanje bitnih informacija, stručni sustavi i sustavi za podršku vezanu za tijek rada.[15] CDSS-i za dijagnozu i liječenje FA-a mogu biti korisni pri uspostavljanju dijagnoze (računalni programi za interpretaciju elektrokardiograma ili interpretaciju 24-satnog ili 48-satnog snimanja elektrokardiograma), pri mapiranju lokacije, biranju terapijskih modaliteta i u praćenju terapije. Jedna od prednosti takvih računalnih sustava jest dostupnost raznovrsnih alata za procjenu rizika, koji su od velike važnosti u terapijskim djelatnostima liječnika.

Svrha je ovoga članka bila opisati razvoj takvog računalnog programa koji će liječnicima omogućiti da provedu brzu procjenu rizika od krvarenja u bolesnika s FA-om kako bi optimizirali primjenu antikoagulacijskog liječenja, pogotovo u onih koji uporabljuju antagoniste vitamina K.

Razvoj računalnoga programa

Računalni je program razvijen u obliku mrežne aplikacije. Responzivni ustroj korisničkog sučelja bio je ključan u postizanju optimalne interakcije korisnika s programom te korisniku omogućuje potpunu kontrolu pri svakom koraku postupka, neovisno o vrsti uređaja koja se primjenjuje, bilo to prijenosno računalo ili pametni telefon. Pozadinski sustav aplikacije razvijen je u programskom jeziku *Python*. Preciznije rečeno, uporabljen je mrežni kostur zvan *Flask*. On se smatra dobrim izborom za brzo prototipiziranje, razvoj i uvođenje malih do srednjih aplikacija. Kako bi se postiglo optimalno korisničko iskustvo na različitim uređajima, sučelje je izrađeno uporabom biblioteke otvorenog koda *Bootstrap*, trenutačno u verziji 4. Aplikacija je smještena na *Heroku* platformi te je dostupna na ovoj poveznici: *https://bleeding-risc-calculator.herokuapp.com/*.

Aplikacija razdvaja postupak odlučivanja u trima koracima. Prikaz prvoga koraka traži od korisnika da izabere vrstu zbroja koji želi izračunati (**slika 1**).

Sljedeći korak uključuje unošenje podataka iz povijesti bolesti, laboratorijskih nalaza, simptoma i komorbiditeta (**slika 2**).

Posljednji ekran prikazuje izračunani zbroj koji pomaže korisniku u odabiru tijeka liječenja (**slika 3**).

The simplest example of the CDSS checks the input data entered by the healthcare professional and checks for values within the reference range. The end result is a certain form of notice or reminder. CDSSs of medium complexity include prognostic calculators and automated guidelines in clinical practice. Prognostic calculators are used for automatic forecasting, usually based on clinical scoring systems. Complex CDSSs use artificial intelligence, data mining, or statistical methods for classifying or predicting a disease or condition of a patient.[14]

These methods automatically identify the key features that are important for clinical classification or anticipation of problems and use mathematical tools to determine the way these characteristics should be combined with the goal of creating output that represents classification or prediction.

CDSS are classified into six categories: medication dosing support, order facilitators, point-of-care alerts/reminders, relevant information display, expert systems, and workflow support systems.[15] CDSSs for atrial fibrillation diagnosis and treatment can be helpful in establishing the diagnosis (software for electrocardiogram interpretation, or 24 or 48 hour ECG Holter monitoring interpretation), mapping the location, in selecting the therapeutic modality, and in the monitoring of the patient's therapy. A benefit of these software systems is the availability of a variety of risk assessment tools, which are of great importance in the therapeutic activities of physicians.

The aim of article was to describe the development of software that will enable clinicians to perform a quick assessment of bleeding risk in patients with AF in order to optimize anticoagulation therapy in patients with AF (especially in patients who use vitamin K antagonists in therapy).

Development of the software

The software was developed in the form of a web application. Responsive design of the interface was key to optimal user interaction, providing seamless control of every step of the process regardless of the type of device used, whether a laptop or a smartphone. The backend of the application was developed in Python. More specifically, a web framework named Flask was utilized. It is considered to be a good choice for rapid prototyping and development and deployment of small- to medium-sized applications. To deliver optimal user experience across different devices, the front-end was built using the Bootstrap open source library, currently in version 4. The application was deployed on the Heroku platform and can be accessed via the following link: *https://bleeding-risc-calculator.herokuapp.com/*.

The process is separated into three steps. The first step prompts the user to select the type of score they want calculated (**Figure 1**).

The following step includes entering anamnestic data, laboratory findings, symptoms, and comorbidities (**Figure 2**).

The final screen displays the calculated score, which assists to user in determining the course of the treatment (**Figure 3**).

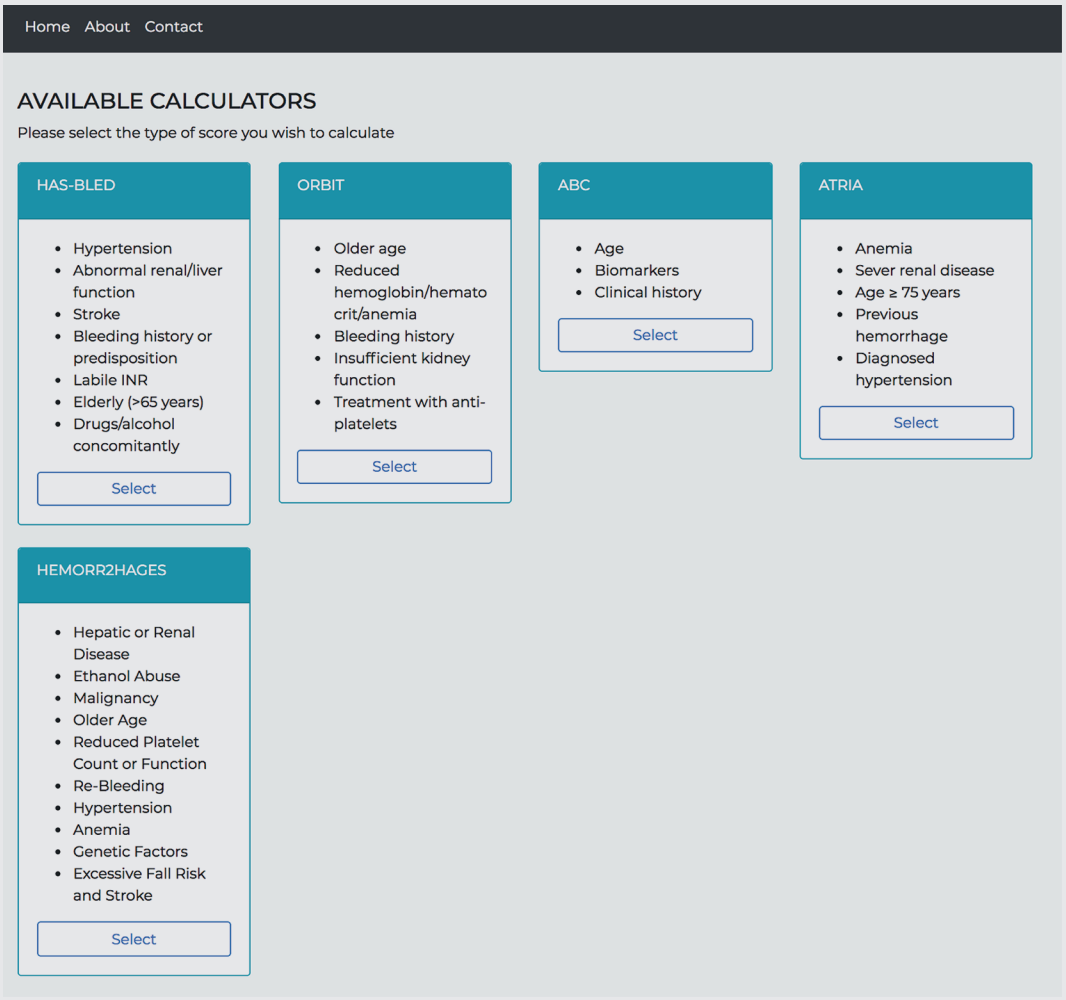

FIGURE 1. First step – the user has to choose which score to use.

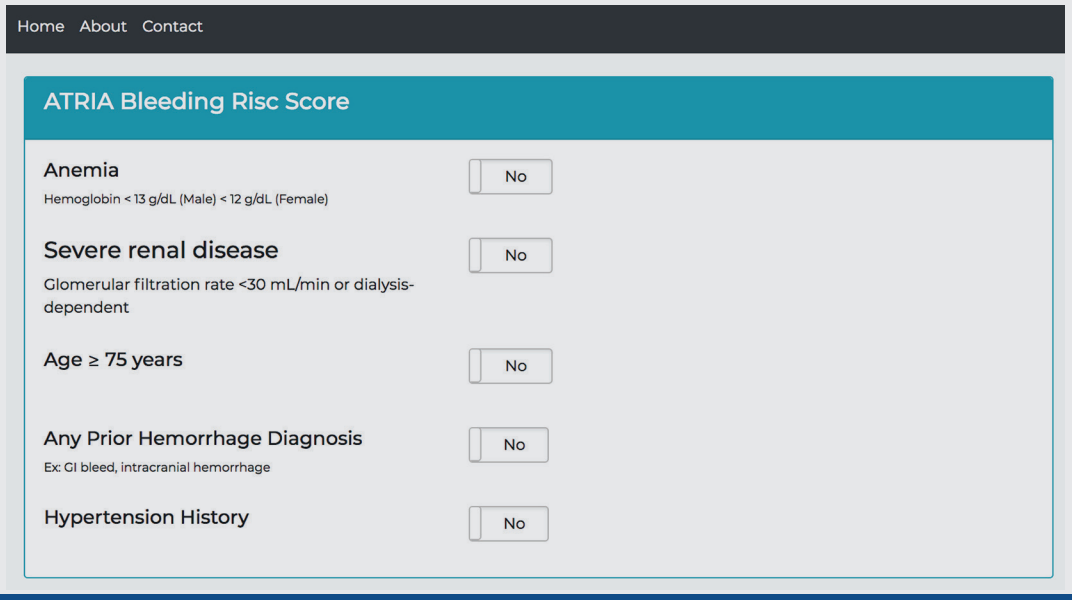

FIGURE 2. Input of data for score calculation.

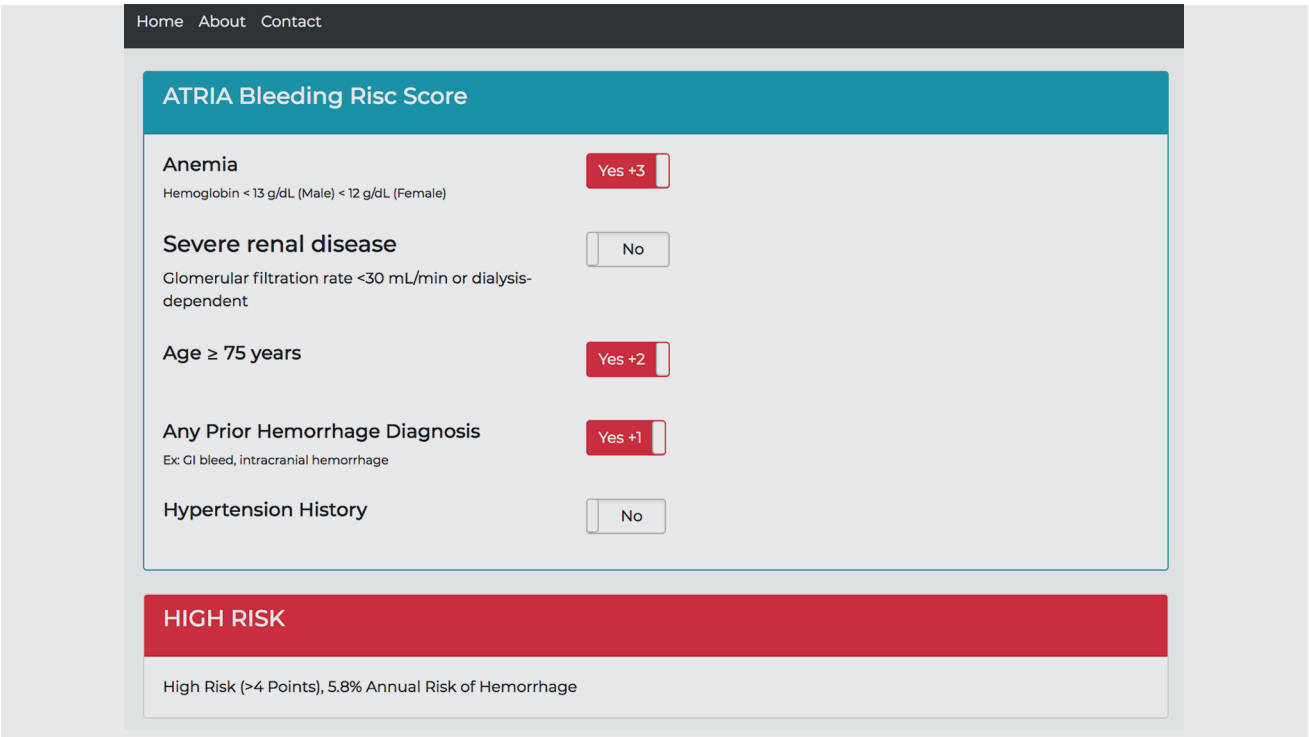

FIGURE 3. Calculated score.

Rasprava

CDSS-i su česti u medicinskoj praksi te u osnovi čine računalno potpomognuti sustav za dijagnosticiranje koji pomaže liječnicima u postavljanju dijagnoze, tijekom liječenja ili u razdoblju praćenja.[14] Njihova je svrha da budu pomoć, a ne zamjena za zdravstvene djelatnike. Istraživanja su pokazala da CDSS-i mogu poboljšati pridržavanje smjernica.[10,16-20] Sheibani *i sur.* utvrdili su da CDSS-i mogu poboljšati pridržavanje antikoagulacijskih smjernica za liječenje FA-a.[21] Primjena CDSS-a poboljšava kvalitetu odluka za specifična pitanja.[22] Procjena optimalne terapije u liječenju FA-a, što uključuje rizik od krvarenja kao najčešće nuspojave liječenja, pogotovo u osoba koji primaju antagoniste vitamina K, traži multidisciplinarni pristup. U bolesnika s vrijednostima INR-a u terapijskim rasponima učestalost hemoragijskih komplikacija manja je od 5 %. Uzimajući u obzir sve parametre koji mogu utjecati na farmakokinetiku i farmakodinamiku, stabilnost lijeka od presudne je važnosti, što se pokatkad podcjenjuje u odabiru liječenja. Izračun rizika primjenom algoritma HAS-BLED pokazao se boljim od HEMORR(2)HAGES i manje praktičnih ATRIA zbrojeva rizika u predviđanju klinički značajnog krvarenja u svakodnevnoj praksi.[11] ORBIT, zbroj rizika od krvarenja s pet elemenata, ima bolju sposobnost predviđanja značajnog krvarenja u bolesnika s FA-om u usporedbi s HAS-BLED i ATRIA alatima.[23,24] Zbroj rizika ABC-stroke pokazao se kao bolji od ostalih te bi mogao pružati poboljšanu podršku pri donošenju odluka pri FA-u.[25] Činjenica da svih pet prije navedenih algoritama pruža dokaze koji podržavaju njihovu uporabu jasno pokazuje da je izbor između njih osobna odluka liječnika, uz poseban oprez koji je nužan u pojedinim populacijama. Izbor zbroja rizika za procjenu krvarenja u kliničkim uvjetima često je osobna odluka te ovisi o praksi

Discussion

CDSSs are common in medical practice, and in essence represent a computer-aided diagnosis systems, which assist physicians in establishing the diagnosis for a patient or directly participate in the process of treatment or in the follow-up period.[14] Their purpose is actually to help physicians, not to replace them. Studies have shown that CDSSs have the potential to improve guideline adherence.[10,16-20] Sheibani *et al.* suggested that CDSSs can improve adherence to the anticoagulation guidelines for the treatment of AF.[21] The use of CDSS tools improves the quality of decision-making for specific issues.[22] Assessment of optimal therapy in the treatment of AF, including risk of bleeding as the most frequent side-effect of therapy, especially in patients who are receiving vitamin K antagonists, requires a multidisciplinary approach to the patient. In patients with INR in therapeutic ranges, incidence of hemorrhagic complications is less than 5%. Taking into account all parameters that may affect the pharmacokinetics and pharmacodynamics, the stability of the drug is of paramount importance, which is sometimes underestimated in treatment choice. HAS-BLED score has been shown to exceed the HEMORR(2)HAGES and less practical ATRIA scores in predicting clinically significant bleeding in everyday practice.[11] The five-element ORBIT bleeding risk score has a better ability to predict major bleeding in AF patients when compared with HAS-BLED and ATRIA risk scores.[23,24] The ABC-stroke score was found to be better than the other risk scores and may provide improved decision support in AF.[25] The fact that all five of the above-mentioned scores have publications that support their use makes it clear that choosing between them will be an individual decision by the physician, with special caution being required in specific populations. Selecting a

samog liječnika. Pametni računalni sustavi primjenjuju se u cjelokupnom postupku pomaganja bolesnicima s FA-om te su uključeni u dijagnozu, liječenje i u praćenje FA-a.[24] Prikazano bi računalno rješenje trebalo pomoći liječnicima u svakodnevnome kliničkom radu ne samo tijekom odabira nego i praćenja pojedinoga terapijskog modaliteta, što bi sprječavalo komplikacije FA-a. Razumijevanje patofiziologije, poboljšanje stratifikacije rizika i individualizirano liječenje imaju izvanrednu važnost u liječenju FA-a.[26]

Primjena računalnih programa koji su lako dostupni i koje su često izradili nemedicinski stručnjaci zahtijeva jasne informacije o referencijama i podatcima na temelju kojih je program napravljen, što je jasno naznačeno u ovome programu. Klinička validacija takvih programa mora biti nešto što je u interesu programskih inženjera, zbog čega je njihov proizvod važan, no također i u interesu liječnika, koji se onda mogu pouzdati u uporabu takvoga programa. Nedostatak spomenutih računalnih programa, uz generacijski otpor prema njihovoj uporabi, jest u tome da izbor primjene određenog algoritma ovisi o kliničkom iskustvu liječnika. Treba uzeti u obzir i i to da izbor alata nije sam po sebi rješenje, nego samo olakšava postizanje rješenja, usto što je, u subjektivnom smislu, naravno i gubitak autoriteta kroz uporabu informacijske tehnologije u kliničkom radu.

Iako su korisnost i potencijal CDSS-a prilično veliki, njihova se primjena još uvijek smatra upitnom, pogotovo među starijim generacijama. Činjenica je da CDSS mora biti utemeljen na točnim, klinički dokazanim informacijama. Učinkovitost CDSS-a potpuno ovisi o snazi dokaza koji su im u pozadini, što znači da se moraju koristiti najnovijim informacijama iz najboljih baza podataka.[15]

Zaključak

Prikazani računalni program jest CDSS koji omogućuje bržu i lakšu procjenu rizika od krvarenja u bolesnika s FA-om, čime se postiže bolji terapijski modalitet. Laka dostupnost takve vrste CDSS-a od velike je pomoći liječnicima u svakodnevnoj praksi te im omogućuje kvalitetnije donošenje odluka glede optimalnoga terapijskog modaliteta. Responzivni ustroj i sučelje u obliku mrežne aplikacije osigurava lako pristupanje programu sa širokog raspona uređaja.

score for assessing the risk of bleeding in clinical conditions is often an individual decision and depends on the practice of the physicians themselves. Smart computer systems are used throughout the process of assisting AF patients and are involved in diagnosis of AF, treatment of AF, and monitoring/follow-up.[24] Our software solution should assist the physician in monitoring/follow-up and should initially be a great help to the physician in the choosing the therapeutic modality itself, which would prevent AF complications. Understanding the pathophysiology, improving risk stratification, and personalizing treatment has outstanding significance in the treatment of AF.[26]

The use of software that is easily accessible and often made by non-medical professionals requires clear information regarding references and data on the basis of which the software was made (this is clearly noted in this software). The clinical validation of such software must be something that is in the interest of the software engineer, which makes their product important, but also in the interest of the physician, who will consequently be confident in using this kind of software. The disadvantage of the software, besides the generational resistance towards its use, is that the choice of using a particular score depends on clinical experience of the physicians. It must also be considered that the choice of the score itself is not a solution and only facilitates the obtainment of a solution, in addition to of course being, in a subjective sense, a loss of authority through the use of information technology in clinical work.

Although the benefits and potential of CDSSs are quite large, their use is still seen as dubious, especially among older generations. The fact is that CDSS must be based on correct, clinically proven information. CDSSs can only be as effective as the strength of the underlying evidence base, meaning that up-to-date information from the best reference databases must be used.[15]

Conclusion

This software represents a CDSS, which enables faster and easier assessment of bleeding risk in patients with AF, leading to a better therapeutic modality. Easy access to this type of CDSS is of great help to physicians in everyday practice and allows them a higher quality decision-making regarding the therapeutic modality of the patient. The responsive design and delivery in the form of a web application makes the software easily accessible on a wide range of devices.

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