Godina 2022. u kardiovaskularnoj medicini: 10 najboljih radova o bolestima srčanih zalistaka

The year in cardiovascular medicine 2022: the top 10 papers in valvular heart disease

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Uvod

Novi članci serije „Godina 2022. u kardiovaskularnoj medicini" donose i nov izazov – kako odabrati samo 10 radova objavljenih u 2022. godini za koje autori smatraju da su upravo oni dali najveći doprinos. Našu smo pretragu ograničili na *New England Journal of Medicine, British Medical Journal, Journal of the American Medical Association, Lancet, European Heart Journal, Circulation i Journal of the American College of Cardiology*. Međutim, ima još radova koji su zavrijedili biti spomenuti. Naš odabir ostaje subjektivan i, osim kvalitete, također smo uzeli u obzir potencijalan utjecaj na kliničku praksu i buduća istraživanja, kao i publikacije za koje smatramo da bi mogle biti od najvećeg interesa našim čitateljima (**Slika 1**).

Introduction

This new format of the 'Year in Cardiovascular Medicine' series brings the challenge to select only 10 papers published in 2022 the authors believe to be the most important in their topic. We restricted our search to the New England Journal of Medicine, British Medical Journal, Journal of the American Medical Association, Lancet, European Heart Journal, Circulation and Journal of the American College of Cardiology. The selection is a consensus of the three authors. There are of course definitely more papers that would deserve to be cited. Our selection remains subjective and besides quality, we also considered the potential impact on clinical practice and future research, as well as publications we felt may be of most interest to our readers (**Figure 1**).

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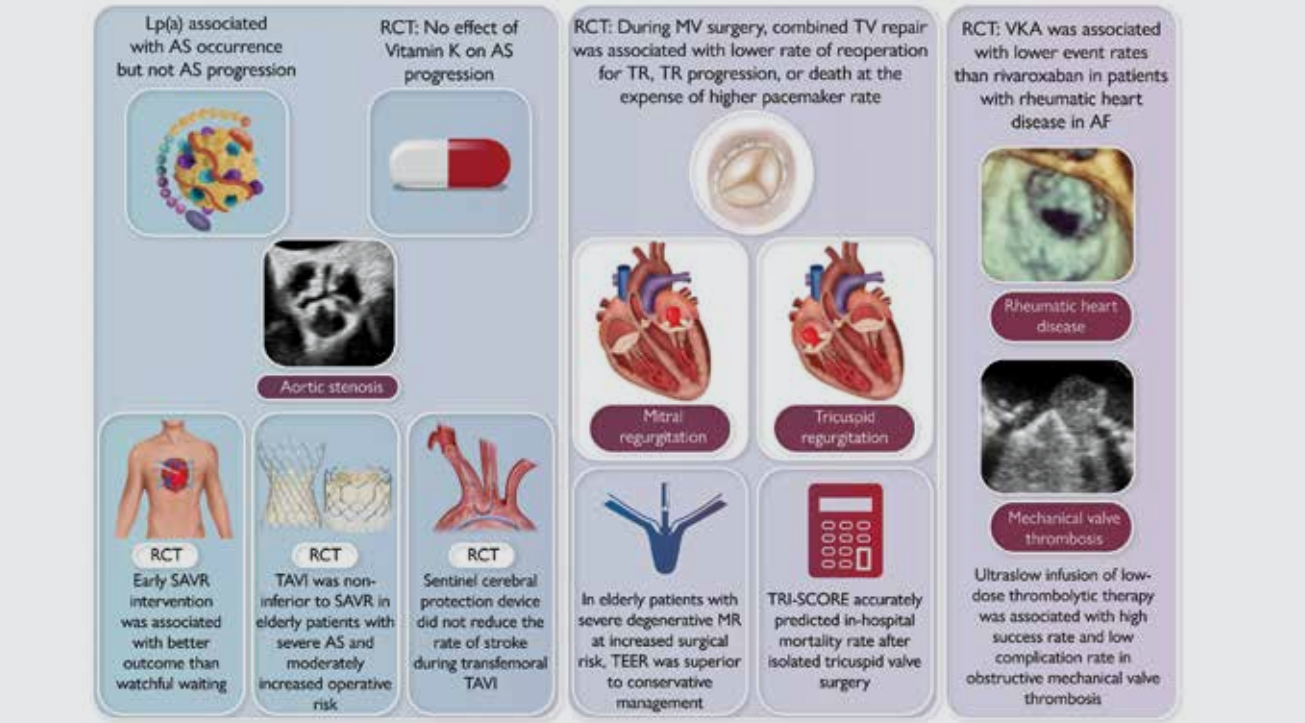

FIGURE 1. Graphical Abstract (from Baumgartner H, Iung B, Messika-Zeitoun D. The year in cardiovascular medicine 2022: the top 10 papers in valvular heart disease. Eur Heart J. 2023;44:551-3. https://doi.org/10.1093/eurheartj/ehac777, by permission of OUP on behalf of the ESC)

Uloga lipoproteina(a) u kalcificiranoj aortalnoj stenozi

Postoje jaki dokazi o uzročnoj-posljedičnoj vezi lipoproteina(a) [Lp(a)] i patogeneze kalcificirane bolesti aortalnog zalistka, iako je njegov utjecaj na progresiju aortalne stenoze (AS) i dalje nejasan. Kaiser *i sur.*[1] ispitivali su povezanost Lp(a) s incidencijom i progresijom kalcificiranosti aortalne valvule (AVC) u 922 bolesnika u istraživanju *Rotterdam Study* s dostupnim mjerenjima Lp(a) i kontrolnim nalazom nekontrastne kompjutorizirane tomografije (prosječno praćenje 14 godina). Kao što je to poznato kod LDL kolesterola i liječenja statinima, tako je i Lp(a) bio snažno povezan s novonastalim kalficikatima aortalne valvule, ali ne i s progresijom kalcifikata aortalne valvule (AVC). Ovi su rezultati važni zbog mogućeg utjecaja na dizajn budućih ispitivanja s lijekovima za snizivanje Lp(a), što pokazuje kako se valja fokusirati na bolesnike s povišenim razinama Lp(a) i/ili fazom prekalcifikacije.

Vitamin K2 i vitamin D u kalcificiranoj aortalnoj stenozi

Vitamin K2 najučinkovitiji je kofaktor za karboksilaciju proteina koji sudjeluju u inhibiciji arterijske kalcifikacije i pretpostavljeno je da bi mogao usporiti progresiju kalcificikacije aortalne valvule. Diederichsen *i sur.*[2] u randomiziranom, placebom kontroliranom istraživanju proučavali su utjecaj 720 µg vitamina K2 uz 25 µg vitamina D dnevno tijekom 24 mjeseca u 365 muškaraca (71 ± 4 godine) s AVC zbrojem >300 AU. Nije bilo razlike u Δ AVC (primarni ishod), ukupno, kao i u skupina bolesnika s AVC zbrojem 300 – 600 ili >600 AU. Iako dobrobit od većih doza i duljeg liječenja ne može biti isključena,

Role of lipoprotein (a) in calcific aortic stenosis

There is strong evidence of a causal role of lipoprotein (a) [Lp(a)] in the pathogenesis of calcific aortic valve disease but its impact on aortic stenosis (AS) progression remained elusive. Kaiser et al.[1] assessed the association of Lp(a) with incidence and progression of aortic valve calcium (AVC) in 922 individuals of the population-based Rotterdam Study with available Lp(a) measurements and repeated non-contrast computed tomography [median follow-up (FU) 14 years]. Like LDL-cholesterol and prior experience with statins, Lp(a) was robustly associated with baseline and new-onset of AVC but not with AVC progression. These results have important implications for the design of future trials with Lp(a) lowering agents suggesting to focus on patients with elevated Lp(a) and/or the pre-calcific disease phase.

Vitamin K2 and D in calcific aortic stenosis

Vitamin K2 is the most effective cofactor for the carboxylation of proteins involved in the inhibition of arterial calcification and has been suggested to reduce the progression of AVC. Diederichsen et al.[2] studied in a randomized, placebo-controlled trial, the effect of 720µg vitamin K2 plus 25µg vitamin D daily over 24 months in 365 men (71±4 years) with an AVC score >300 arbitrary units (AU). There was no difference in ΔAVC score (primary outcome), overall and in subsets with AVC scores 300–600 or >600 AU. Although the potential benefit of higher dosages and longer treatment duration cannot be excluded, this study rather discourages further trials with vitamin K2.

ovo se istraživanje ne zalaže za daljnje ispitivanje vitamina K2 u navedene svrhe.

Zamjena aortalnog zalistka u bolesnika s asimptomatskom aortalnom stenozom

Kada operirati bolesnika s asimptomatskom AS, ostaje i dalje nejasno. U istraživanju *AVATAR*[3] u 157 ispitanika s asimptomatskom teškom AS, potvrđenom negativnim testom opterećenja uz očuvanu ejekcijsku frakciju lijeve klijetke, provedena je randomizacija u dvije skupine – bolesnici liječeni ranim kardiokirurškim zahvatom ili oni liječeni konzervativno. Nakon 32 mjeseca praćenja operirani su bolesnici imali mnogo nižu incidenciju (15 % *vs.* 35 %) primarnog zajedničkog ishoda (ukupna smrtnost, akutni infarkt miokarda, moždani udar, neplanirana hospitalizacija zbog zatajivanja srca) u usporedbi s onima koji su bili liječeni konzervativno. Nije bilo razlike u kardiovaskularnom mortalitetu (9,5 % *vs.* 9,1 %), dok je ukupna smrtnost pokazivala tendenciju sniženja (10 % *vs.* 20%, P = 0,16). Ovi rezultati zahtijevaju daljnju potvrdu u većim istraživanjima, a u iščekivanju su rezultati istraživanja koje uspoređuju transkateterski i kirurški pristup – sve sa svrhom pravodobnog prepoznavanja skupine bolesnika koji bi mogli imati najviše koristi od rane intervencije (npr. fibroza miokarda).

Transkateterska *vs.* kirurška zamjena aortalnog zalistka kod aortalne stenoze

Koji modalitet liječenja AS-a odabrati, i dalje ostaje nepoznanica. Provedeno je randomizirano istraživanje *UK transcatheter aortic valve implantation (TAVI)*[4], koje je za primarni ishod imalo ukupnu smrtnost, a uključivalo je 913 bolesnika starijih od 70 godina (medijan 81 godina) sa simptomatskom teškom AS i niskim do umjerenim operativnim rizikom (medijan STS zbroja 2,6 %). Navedeno je istraživanje potvrdilo neinferiornost TAVI-ja u usporedbi s klasičnim kirurškim zahvatom. Nije bilo statistički značajne razlike u moždanom udaru, dok je učestalost teških krvarenja bila veća u bolesnika u kojih je učinjena kirurška zamjena aortalnog zalistka, a učestalost vaskularnih komplikacija, potrebe za ugradnjom trajnog elektrostimulatora srca i paravalvularne regurgitacije bila je veća u bolesnika liječenih s pomoću TAVI-ja. U usporedbi s ranijim istraživanjima, ovo je istraživanje pragmatično, javno financirano i dizajnirano za usporedbu TAVI-ja, primjenjujući bilo koju vrstu valvule i pristupa u usporedbi s klasičnim kirurškim pristupom u širokog raspona bolesnika.

Zaštita od cerebralne embolizacije tijekom transkateterske implantacije aortalnog zalistka

Moždani udar zbog embolizacije debrisa tijekom procedure TAVI potencijalno je teška komplikacija. Kapadia *i sur.*[5] randomizirali su 3000 bolesnika podvrgnutih transfemoralnoj TAVI proceduri u dvije skupine – na bolesnike u kojih jest ili nije primjenjivan uređaj *Sentinel embolic protection device*. Uporaba navedenog uređaja pokazala se sigurnom, dok je incidencija svih moždanih udara unutar 72 sata postintervencijski ili neposredno prije otpusta (primarni ishod) bila snižena, ali se nije razlikovala između dviju ispitivanih skupina bolesnika (2,3 % *vs.* 2,9 %). Nijedna podskupina, ni prema dobi ili potencijalnim čimbenicima rizika, nije pokazala dobrobit zaštite od cerebralne embolije. Navedeno istraživanje ne podupire rutinsku primjenu zaštitnih uređaja u svrhu prevencije embolije. Individualizirani pristup u visokorizičnih bolesnika i njihov utjecaj na moždani udar zaslužuje daljnju evaluaciju.

Aortic valve replacement in asymptomatic aortic stenosis

The timing of surgery in asymptomatic AS remains controversial. In the AVATAR Trial,[3] 157 patients with severe asymptomatic AS confirmed by a negative exercise test and preserved left ventricular ejection fraction (LVEF) were randomly allocated to early surgery or conservative treatment. After a median FU of 32 months, the early surgery group had a significantly lower incidence (15 vs. 35%) of the primary composite endpoint (all-cause mortality, acute myocardial infarction, stroke, or unplanned hospitalization for heart failure) than the conservative treatment group. There was no difference in cardiovascular deaths (9.5 vs. 9.1%) but a trend towards lower all-cause death (10 vs. 20%, P=0.16). These results require confirmation in larger populations, ongoing studies evaluating transcatheter therapies instead of surgery, and the identification of subsets that might benefit the most from an early intervention strategy (e.g. myocardial fibrosis).

Transcatheter aortic valve implantation vs. surgical aortic valve replacement for aortic stenosis

The choice of treatment modality for AS remains controversial. The randomized UK transcatheter aortic valve implantation (TAVI) Trial[4] with the primary endpoint of all-causemortality included 913 patients aged 70 years or older (median 81 years) with severe symptomatic AS and low-to-moderate operative risk (median STS score 2.6%). The trial confirms the non-inferiority of TAVI. There was no difference in stroke, and the rate of severe bleeding was higher with surgical aortic valve replacement, while vascular complications, pacemaker implantation, and paravalvular regurgitation were more frequent with TAVI. In contrast to previous trials, this trial was pragmatic, publicly funded, and designed to compare a TAVI strategy using any valve type and access route vs. surgery in a broad range of patients included according to clinical equipoise regarding the treatment options and not bound by prespecified risk score.

Cerebral embolic protection during transcatheter aortic valve implantation

Stroke due to embolization of debris during the procedure remains a devastating complication of TAVI. Kapadia et al.[5] randomized 3000 transfemoral TAVI patients to use or no use of the Sentinel embolic protection device. The use of the protection device appeared to be safe but the incidence of all stroke within 72 h post-intervention or before discharge (primary endpoint) was overall low and did not differ between groups (2.3 vs. 2.9%). No subgroup by age or potential risk factors could be identified that demonstrated a benefit of cerebral embolic protection. This study does not support the routine use of embolic protection devices. A more selective individualized approach in high-risk–risk patients and its impact on disabling stroke deserve further evaluation.

Transcatheter edge-to-edge repair (TEER) in older patients with severe, symptomatic degenerative mitral regurgitation

Current guidelines recommend TEER in patients with severe degenerative mitral regurgitation (DMR) deemed inoperable or at high risk for surgery without definitive evidence. It is, however, unlikely that a randomized trial will ever be con-

Transkateterska *edge-to-edge repair* (TEER) u starijih bolesnika s teškom, simptomatskom degenerativnom mitralnom regurgitacijom

Trenutačno važeće smjernice preporučuju primjenu TEER-a u bolesnika s teškom degenerativnom mitralnom regurgitacijom (DMR) koji su inoperabilni ili imaju visok kirurški rizik bez sigurnih dokaza. Malo je vjerojatno da će se ikada provesti randomizirano kliničko istraživanje koje uspoređuje TEER (trenutno klasa II. preporuke za visokorizične bolesnike s primarnom MR) i medikamentno liječenje. Benfari *i sur.*[6] analizirali su rezultate iz velikih registara (MitraSwiss, Minneapolis Heart Institute, MIDA) koji su uključivali 1187 bolesnika starijih od 65 godina sa simptomatskom teškom DMR. Pokazano je da je TEER povezan s nižim mortalitetom prilagođenim za dob, spol, EuroSCORE II, NYHA klasom, fibrilacijom atrija i ejekcijskom frakcijom lijeve klijetke. Nakon podudarnog spajanja (247 parova sa srednjim EuroSCORE-om II od 3,0 %) TEER je i dalje pokazao bolje preživljenje u usporedbi s neoperiranim bolesnicima (49 ± 6 *vs.* 37 ± 3 % u 4 godine). U ovom registru neuspjeh procedure kod iskusnih operatera bio je rijedak, ali povezan s učestalijom smrtnošću. Ovi nalazi upućuju na proširenje indikacija za TEER u bolesnika starijih od 65 godina s teškom DMR, osim trenutačnih – u inoperabilnih i visokorizičnih bolesnika.

Predviđanje mortaliteta nakon izolirane operacije trikuspidalnog zalistka

Izolirani kirurški zahvat trikuspidalne valvule (ITVS) u nekongentalne teške trikuspidalne regurgitacije smatra se visokorizičnom procedurom, a ishod znatno varira ovisno o karakteristikama bolesnika te je adekvatna procjena rizika od velike važnosti pri postavljanju indikacije za operativni zahvat. Dreyfus *i sur.*[7] obradili su podatke dobivene od 466 bolesnika koji su podvrgnuti ITVS-u. Oni su izveli i validirali nov sustav bodovanja (TRI-SCORE – http://www.tri-score.com/) za procjenu rizika od unutarbolničkog mortaliteta. Sustav bodovanja temelji se na osam varijabli: životna dob >70 godina, NYHA klasa III. – IV., znakovi desnostranog zatajivanja srca, dnevna doza furosemida >125 mg, glomerularna filtracija <30 mL/min, povišena razina bilirubina, ejekcijska frakcija lijeve klijetke <60 % i umjereno teška / teška disfunkcija desne klijetke. Ovaj rezultat koristi se lako dostupnim varijablama i može služiti u procesu donošenja odluka o modalitetu liječenja u bolesnika s teškom TR.

Istodobni popravak trikuspidalnog zalistka u bolesnika s degenerativnom mitralnom regurgitacijom

Istodobni popravak trikuspidalnog zalistka (TVR) široko se preporučuje u bolesnika koji se podvrgavaju operaciji mitralnog zalistka (MV) jer se pokazalo da je teška trikuspidalna insuficijencija važan uzrok kasnog morbiditeta i mortaliteta, iako uz slabe dokaze. Gammie *i sur.*[8] su 401 bolesnika s umjereno teškom TR ili blažim stupnjem TR, ali uz anularnu dilataciju koji su planirani za kirurški zahvat mitralnog zalistka zbog DMR-a, randomizirali u 2 skupine: kirurški zahvat MV s TVR-om ili bez njega. Primarni je zajednički dvogodišnji ishod (reoperacija zbog TR-a, progresija TR-a za dva stupnja u odnosu prema početnom, prisutnost teške TR ili smrtni ishod) postignut, no uvelike na temelju progresije TR-a (pogotovo u bolesnika s početno umjereno teškom TR), dok se mortalitet i morbiditet nisu značajno razlikovali između ispitivanih skupina bolesnika. Bolesnici s istodobnom TVR imali su mnogo višu stopu implantacije trajnog elektrostimulatora srca. Ostaje

ducted to compare TEER, which is a Class II recommendation in high-risk patients with primary MR, with medical therapy. Benfari et al.[6] analysed large registries (MitraSwiss, Minneapolis Heart Institute, MIDA) including 1187 patients≥65 years with symptomatic severe DMR. TEER was associated with lower mortality adjusted for age, sex, EuroSCORE II, NYHA class, atrial fibrillation, and LVEF. After propensity matching (247 pairs with median EuroSCORE II of 3.0%), TEER consistently showed better survival compared with unoperated patients (49±6 vs. 37±3% at 4 years).

Procedural failure was infrequent in this registry of experienced operators but associated with excess mortality. These findings suggest extending indications of TEER in patients aged older than 65 years with severe DMR beyond the current recommendation in inoperable or high-risk patients.

Prediction of mortality after isolated tricuspid valve surgery

Isolated tricuspid valve surgery (ITVS) in non-congenital severe tricuspid regurgitation (TR) is considered a high-risk procedure but outcomevaries markedly depending on patient characteristics and appropriate risk assessment is crucial for decision-making. From data of 466 consecutive patients undergoing ITVS, Dreyfus et al.[7] derived and internally validated a new scoring system (TRI-SCORE – http://www.tri-score.com/) for in-hospital mortality prediction based on eight variables: age ≥70 years, NYHA Class III–IV, right-sided heart failure signs, daily dose of furosemide ≥125 mg, glomerular filtration rate <30 mL/min, elevated bilirubin, LVEF <60%, and moderate/severe right ventricular dysfunction. The TRI-SCORE provided excellent discrimination and calibration with observed and predicted in-hospital mortality increasing from 0% to 60% and from 1% to 65% with a score increase from 0 to ≥9. This score using easily available variables may guide the clinical decision-making process of patients with severe TR.

Concomitant tricuspid valve repair in patients with degenerative mitral regurgitation

Concomitant tricuspid valve repair (TVR) is liberally recommended in patients undergoing mitral valve (MV) surgery as persistent or developing severe TR has been demonstrated to be an important cause of late morbidity and mortality, but the evidence is weak. Gammie et al.[8] randomly assigned 401 patients with moderate TR or less-than-moderate TR but annular dilatation undergoing MV surgery for DMR to a mitral procedure with or without TVR. The primary 2-year endpoint—a composite of reoperation for TR, progression of TR by two grades from baseline or the presence of severe TR, or death was met but mainly driven by the progression of TR (particularly in patients with moderate TR at baseline) while mortality and morbidity were not significantly different. Remarkably, the patients with concomitant TVR had a significantly higher pacemaker implantation rate. While the latter remains a matter of concern, the negative impact of significant TR occurrence on long-term outcomes may not be detected with the short FU of 2 years.

Thombolysis or surgery in patients with obstructive mechanical valve thrombosis

The optimal treatment of obstructive mechanical valve thrombosis remains controversial. Current guidelines favour

upitno je li razdoblje praćenja od 2 godine dovoljno za demarkiranje negativnog učinka značajne TR na dugoročne ishode.

Tromboliza ili kirurški zahvat u bolesnika s opstruktivnom mehaničkom trombozom zalistka

Optimalno liječenje opstruktivne mehaničke tromboze zalistaka ostaje kontroverzno. Trenutačne smjernice prednost daju kirurgiji sve dok se može izvesti uz prihvatljiv rizik. Özkan *i sur.*[9] proveli su istraživanje uspoređujući ishod trombolitičke terapije (TT) koristeći se sporom (6 sati) i/ili ultrasporom (25 sati) infuzijom niske doze tkivnog aktivatora plazminogena – 25 mg) i kirurškog zahvata. Uspješnost TT-a bila je 90 %. Učestalost incidenata u kirurškoj (n = 75) i TT (n = 83) grupi bile su male komplikacije 39 % *vs.* 8 %, velike komplikacije 41 % *vs.* 6 %, tromjesečni mortalitet 19 % *vs.* 2 %. Iako je navedeno istraživanje opservacijsko s inherentnom selekcijom i pristranošću i malim brojem ispitanika, visoka stopa uspješnosti i niska stopa komplikacija TT-a može utjecati na našu praksu u liječenju opstruktivne stenoze zalistka.

Direktni oralni antikoagulansi kod fibrilacije atrija povezane s reumatskom bolesti srca

Bolesnici s reumatskom mitralnom stenozom i fibrilacijom atrija (FA) bili su isključeni iz prethodnih istraživanja koja su uspoređivala antagoniste vitamina K (VKA) i neantagoniste vitamina K u liječenju FA-a. Istraživanje *INVICTUS*[10] randomiziralo je 4565 bolesnika s reumatskom bolešću srca i pridruženom FA (prosječne životne dobi 51 godina, 72 % žene, 85 % s mitralnom stenozom) u dvije skupine: jedna skupina bolesnika primala je standardnu dozu rivaroksabana, a druga prilagođenu dozu antagonista vitamina K. Neočekivano, terapija VKA-om rezultirala je nižom učestalošću primarnog ishoda (zbroja kardiovaskularnih ishoda ili smrtnog ishoda), moždanog udara, ukupnog mortaliteta, iznenadne smrti u usporedbi s rivaroksabanom, a bez većeg rizika od krvarenja. Moguća objašnjenja za navedene rezultate uključuje nižu učestalost moždanog udara od očekivane, čime se smanjuje snaga ispitivanja, pomnije kliničko praćenje i bolja suradljivost u skupini koja je primala VKA. Razlike u mortalitetu bile su velike. Opisano istraživanje podržava trenutačne preporuke o uporabi VKA-a u bolesnika s mitralnom stenozom i fibrilacijom atrija.

surgery as long as it can be performed with acceptable risk. Özkan et al.[9] aimed to prospectively evaluate the outcomes of thrombolytic therapy (TT) using slow (6 h) and/or ultraslow (25 h) infusion of low-dose tissue plasminogen activator (25 mg) and surgery. The success rate of TT was 90%. Event rates in the surgical (n = 75) and TT (n = 83) groups were as follows: minor complications 39 vs. 8%, major complications 41 vs. 6%, and 3-month mortality 19 vs. 2%, respectively. Although the study is observational with inherent selection and confounding bias and the number of patients is relatively small, the high success rate and markedly low complication rate of the proposed TT regime may influence our practice in obstructive mechanical valve thrombosis.

Non-vitamin K antagonist oral anticoagulation in rheumatic heart disease associated atrial fibrillation

Patients with rheumatic mitral stenosis and AF were excluded from prior studies comparing vitamin K antagonists (VKAs) and non-vitamin K antagonist oral anticoagulation in AF. The INVICTUS trial[10] randomly assigned 4565 patients with rheumatic heart disease associated atrial fibrillation (mean age: 51 years, 72% women and 85% with mitral stenosis) to standard doses of rivaroxaban or dose-adjusted VKA (open-label trial with blinded assessment of outcomes). Unexpectedly, VKA therapy led to lower rates of the primary endpoint (composite of cardiovascular events or death), stroke, all-cause death, and sudden death than rivaroxaban, without a higher bleeding rate. Possible explanations for these findings include the lower-than-expected stroke rate thereby reducing trial power, closer clinical monitoring, and better compliance in theVKAgroup. Differences in mortality were large and unlikely to be due to chance. The study supports current recommendations of VKA use in mitral stenosis.

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