Godina 2017. u kardiologiji: aorta i periferna cirkulacija

The year 2017 in cardiology: aorta and peripheral circulation

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CITATION: Cardiol Croat. 2018;13(3-4):99-109. | https://doi.org/10.15836/ccar2018.99

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TO CITE THIS ARTICLE: Aboyans V, Braekkan S, Mazzolai L, Sillesen H, Venermo M, De Carlo M; ESC Working Group on Aorta and Peripheral Vascular Diseases. The year 2017 in cardiology: aorta and peripheral circulation. Cardiol Croat. 2018;13(3-4):99-109. DOI: 10.15836/ccar2018.99

TO LINK TO THIS ARTICLE: https://doi.org/10.15836/ccar2018.99

Uvod

U zemljama članicama Europskoga kardiološkog društva (ESC) živi više od 83 milijuna ljudi s kardiovaskularnim (CV) bolestima, od čega je perifernom vaskularnom bolesti najčešće stanje (u više od 35 milijuna oboljelih), a potom slijedi ishemijska bolest srca (>29 milijuna), čineći važan javnozdravstveni teret na našem kontinentu.[1]

ESC je u suradnji s Europskim društvom za vaskularnu kirurgiju (ESVS) objavio najiscrpniji dokument sa smjernicama za postupanje pri perifernim arterijskim bolestima (engl. *peripheral arterial diseases*, PADs), obuhvaćajući sve periferne teritorije.[2] U usporedbi s inačicom iz 2011. godine, značajne promjene uključuju stratifikaciju rizika u pacijenata s asimptomatskom bolesti karotida i u onih s kritičnom ishemijom koja ugrožava udove (engl. *critical limb-threatening ischaemia*, CLTI) te novo, specifično poglavlje o bolestima srca u pacijenata s PADs. Svaka vrsta prezentacije PADs povezana je s vrlo visokim rizikom za CV događa-

Preamble

More than 83 million people live with cardiovascular (CV) disease in the ESC member countries, with peripheral vascular diseases as the most predominant condition (more than 35 million) followed by ischaemic heart disease (>29 million), underlining the public health burden of the former in our continent.[1]

The ESC collaborated with European Society of Vascular Surgery (ESVS) to publish the most comprehensive guidelines document on the management of peripheral arterial diseases (PADs), encompassing all the peripheral territories.[2] Compared to the 2011 version, major changes regard risk stratification for patients with asymptomatic carotid disease, and those with critical limb-threatening ischaemia (CLTI), and a new specific chapter on cardiac diseases in patients with PADs. Any presentation of PADs is associated with a very high risk for CV events, and all patients require best medical therapy for sec-

RECEIVED:
February 28, 2018
ACCEPTED:
March 1, 2018

je i svim je pacijentima potrebna optimalna medikamentna terapija u svrhu sekundarne prevencije. U tom kontekstu studija VIVA[3] i COMPASS[4] predstavljaju dva ključna randomizirana klinička ispitivanja (engl. *randomized controlled trials*, RCTs).

Studija VIVA pokazala je korist od višestrukih vaskularnih probira u produljenju dugovječnosti populacije (**tablica 1**).[3] Više od 50 000 danskih muškaraca bilo je randomizirano na one koji su dobili poziv za probir i na one koji nisu. Vaskularni se probir sastojao od nadlaktičnoga mjerenja arterijskoga tlaka i pedobrahijalnog indeksa (engl. *ankle brachial index,* ABI) te ultrazvuka abdominalne aorte. Pacijenti s pozitivnim nalazima bili su pozvani da se jave svojem liječniku primarne zdravstvene zaštite, dok su oni s velikim aneurizmama abdominalne aorte (AAA) upućeni vaskularnim kirurzima. Nakon 4,4 godine praćenja smrtnost je bila mnogo niža u skupini koja je bila podvrgnuta probiru (**tablica 1**). Broj potrebnih pregleda za sprječavanje jednoga smrtnog ishoda bio je 169, mnogo manji od bilo kojega broja u probirima za bilo koju malignu bolest.

U studiji COMPASS bilo je randomizirano 27 395 pacijenata koji su imali ili koronarnu bolest srca (CAD) ili PAD [arterijsku bolest donjih udova (LEAD) ili stenozu karotidne arterije ili pak prethodnu karotidnu revaskularizaciju] u skupine s tri različite antitrombocitne strategije. U predefiniranoj podanalizi pacijenata s PAD-om rezultati su bili konzistentni s onima u cjelokupnoj populaciji (**tablica 1**): kombinacija rivaroksabana 2,5 mg dvaput na dan + acetilsalicilatna kiselina (ASK) 100 mg bila je povezana sa znatnim 28 %-tnim smanjenjem kombiniranog ishoda od CV smrti, infarkta miokarda ili moždanog udara te s 46 %-tnim smanjenjem velikih neželjenih događaja vezanih za udove (engl. *major adverse limb events*, MALE), uključujući amputacije, u usporedbi s ASK 100 mg.[4] Krvarenja su bila češća uz kombiniranu terapiju, osim fatalnih krvarenja. Netokorist, uključujući ishemijske događaje i velika krvarenja, ostala je na strani kombinirane terapije. Kliničke implikacije za postupanje s takvim pacijentima zahtijevaju dodatne analize kako bi se odabrale specifične podskupine s optimalnim omjerom koristi/rizika (RR). Također, važna je vanjska primjenjivost ovih rezultata: među sudionicima REACH studije koji su imali LEAD, bilo je 68 % kompatibilnih sa studijom COMPASS, ispunjavajući kriterije uključivanja i isključivanja.[15] Glavni razlog za nekompatibilnost s COMPASS studijom bio je visok rizik od krvarenja. Stoga stratifikacija rizika od krvarenja ima najveću važnost.

Druge specifične studije arterijske bolesti donjih udova

Smjernice ESC iz 2017. godine[1] ističu važnost optimalnog zbrinjavanja čimbenika rizika u bolesnika s PADs. Nova analiza studije FOURIER naglasila je važnost snizivanja vrijednosti LDL kolesterola u pacijenata s LEAD-om, uz značajnu dobrobit (**tablica 1**) primjenom evolokumaba (inhibitor PCSK-9).[7] Ta nova analiza u pacijenata s LEAD-om pokazala je sličnu dobrobit u snizivanju učestalosti CV događaja i znatno sniženje MALE. To je prva studija koja je pokazala korist od hipolipemika u sniženju MALE, uključujući amputaciju.

Mnogi su pacijenti s LEAD-om dijabetičari. Nedavno su prikazani upadljivo pozitivni rezultati CV dobrobiti od primjene inhibitora suprijenosnika natrija i glukoze 2, iako je povećani rizik za amputaciju uz kanaglifozin (većinom manjega stupnja) izazvao zabrinutost.[16] Nova analiza pacijenata s LEAD-om koji su bili uključeni u studiju EMPA-REG potvrdila je

ondary prevention. In this respect, the VIVA[3] and COMPASS[4] trials are definitely the two seminal randomized controlled trials (RCTs) of the year.

The VIVA trial demonstrated the interest of multiple vascular screening to improve population longevity (**Table 1**).[3] Over 50 000 Danish men were randomized to receive an invitation for vascular screening or not. Vascular screening consisted of arm blood pressure and ankle-brachial index (ABI) measurement, and abdominal aorta ultrasound. Positive cases were invited to consult their general practitioners, while large abdominal aorta aneurysm (AAA) were referred to vascular surgeons. After 4.4 years, the mortality was significantly lower in the screening group (**Table 1**). The number needed to screen to prevent one death was 169, far below the one necessary for any cancer screening.

The COMPASS trial randomized 27 395 patients either with coronary artery disease (CAD) or PADs [lower-extremity artery disease (LEAD) or carotid stenosis or prior carotid revascularization] to three different antithrombotic strategies. In the pre-defined sub-analysis of patients with PADs, the results were consistent with those obtained in the entire population (**Table 1**): the combination of rivaroxaban 2.5 mg b.i.d. + aspirin 100 mg was associated with a significant 28% reduction of a combination of CV death, myocardial infarction, or stroke and a 46% reduction of major adverse limb events (MALE), including amputation, as compared to aspirin 100 mg.[4] Bleeding events were higher under the combination therapy, except for fatal bleeding. The net benefit including ischaemic and major bleeding events remained in favour of the combination strategy. The clinical implication for the management of these patients needs further analyses to select specific subgroups with an optimal benefit/risk ratio (RR). Also, the external applicability of these results is important; among REACH participants with LEAD, 68% were COMPASS-compatible, fulfilling inclusion, and exclusion criteria.[15] The main reason for not being COMPASS-compatible was a high-bleeding risk. Hence, the bleeding risk stratification is of paramount importance.

Other specific studies in lower-extremity artery disease

The 2017 ESC guidelines[1] emphasize the optimal management of risk factors in patients with PADs. A new analysis of the FOURIER trial underscored the importance of lowering LDL-cholesterol in patients with LEAD, with significant benefits with evolocumab, a PCSK-9 inhibitor (**Table 1**).[7] This new analysis in patients with LEAD showed similar benefits in terms of CV events reduction, and a significant reduction of MALE. This is the first trial showing the benefits of a lipid-lowering drug to reduce MALE, including amputation.

Many patients with LEAD are diabetic. Recently strikingly positive results on the CV benefits of sodium glucose cotransporter 2-inhibitors have been presented, although concerns were raised regarding the increased risk of amputation (mostly minor) with canaglifozin.[16] A new analysis of patients with LEAD enrolled in the EMPA-REG trial confirmed the benefits of empagliflozin in terms of mortality and CV events (**Table 1**), without any difference in amputation rates as compared to placebo.[6] The need for improved diabetes care was underlined by a recent registry on 15 332 CLTI patients (47% diabetic), showing that in spite of a 60% higher risk of infec-

TABLE 1. Summary of major randomized trials in peripheral intervention in 2017.

Trial's acronym (or first author)	Type and aim of the study	Challenger (n)	Reference (n)	Setting (indication)	Primary outcome (+ secondary outcomes of interest)
Multiple localization					
COMPASS-PAD[4]	Double-blind: interest of low-dose rivaroxaban (alone or with aspirin) in patients with PADs	Rivaroxaban 2.5 mg x 2 + Aspirin 100 mg (R + A: 2492) or Riva 5 mg x 2 (R: 2474)	Aspirin 100 mg (A: 2504)	LEAD (past revascularization, claudication with proven LEAD, or CAD with ABI < 0.90) or carotid disease (past revascularization or carotid stenosis > 50%)	CV death, MI or Stroke: R+A vs. A = -28% (P = 0.0047); R vs. A = −14% (P = 0.19). -46% reduction of MALE for R + A vs. A. +61% bleeding risk, but not fatal bleeding.
VIVA[3]	Open: interest of vascular screening in general population	Screening for hypertension, LEAD and AAA (25 078)	No screening (25 078)	Men aged 65–74 years in Central Denmark	Mortality (HR 0.93; 95% CI 0.88–0.98)
Carotid artery disease					
Moresoli[5]	Meta-analysis: CAS versus CEA in patients with asymptomatic carotid stenosis	CAS (1881)	CEA (1138)	Asymptomatic carotid stenosis	Any peri-procedural stroke and long-term stroke (RR 1.24; 95% CI 0.76–2.03) or death (RR 1.72; 95% CI 0.95–3.11)
Lower extremities artery disease					
EMPA-REG (LEAD subgroup)[6]	Double-blind: efficacy and safety of empagliflozin on top of standard care in type 2 diabetic patients with LEAD	Empagliflozin (982)	Placebo (479)	LEAD (past revascularization or amputation, stenosis > 50%, or ABI < 0.90)	CV death: HR, 0.57; 95%CI, 0.37–0.88. -38% all-cause mortality reduction No increased risk of amputation.
FOURIER (LEAD subgroup)[7]	Double-blind: interest of evolocumab on top of statins to reduce cardiovascular events	Evolocumab (1856)	Placebo (1780)	Claudication and ABI < 0.85 or prior revascularization	Composite: CV death, MI, stroke, hospitalization for unstable angina, or coronary revascularization: −21% (P < 0.01). MALE also reduced by − 42% (P < 0.01)
ICE[8]	Open: SES vs. BES for iliac occlusive disease	SES (340)	BES (320)	Moderate to severe claudication caused by iliac artery stenosis or occlusion	Binary restenosis at 12 months 6.1% (SES) vs. 14.9% (BES) P = 0.006
ISAR-STATH[9]	Open: endovascular techniques for superficial femoral artery revascularization	DCB + stent (48) or atherectomy (52)	BMS (55)	stenosis or occlusion of superficial femoral artery	(1) Diameter stenosis in percentages measured by angiography 34%. 56% vs. 55%; P = 0.009 and 0.007; (2) Binary restenosis rate 7.23% vs. 22.52% vs. 24.54%; P = 0.0017 PEB + stent vs. BA + stent
ILLUMENATE pivotal[10]	Single-blind: DCB vs. PTA in femoropopliteal disease	DCB (200)	PTA (100)	Rutherford Class 2–4 LEAD caused by femoropopliteal stenosis or occlusion	(1) Composite: 12 months of freedom from device and procedure-related 30 days of death, and from target limb major amputation and CD-TLR: 92.1% vs. 83.2% P = 0.001; (2) 12 monthsa primary patency 76.3% vs. 57.6% P = 0.003
ILLUMENATE EU[11]	Single-blind: DCB vs. PTA in femoro-popliteal disease	DCB (222)	PTA (72)	Moderate to severe claudication or ischemic rest pain caused by femoro-popliteal stenosis or occlusion	(1) Composite: 30 days of freedom from device- and procedure-related death, and 12 monthsb from target limb major amputation and CD-TLR: 94.1% vs. 83.3%. (2) Primary patency 12 monthsb and freedom from CD-TLR 83.9% vs. 60.6% P = 0.001

TABLE 1. Summary of major randomized trials in peripheral intervention in 2017 (continued).

Trial's acronym (or first auther)	Type and aim of the study	Challenger (n)	Reference (n)	Setting (indication)	Primary outcome (+ secondary outcomes of interest)
Venous thrombo-embolic disease					
EINSTEIN-choice[12]	Double-blind: Efficacy & safety of two doses of rivaroxaban vs. aspirin in long-term after VTE	Rivaroxaban 10 mg OD (R10: 1127)	Aspirin 100 mg OD (A: 1131)	After 6–12 months of anticoagulation for acute DVT or PE	Symptomatic recurrent fatal or nonfatal VTE
		Rivaroxaban 20 mg OD (R20: 1107)			R20 vs. A: −66% (P < 0.001)
					R10 vs. A: −74%(P < 0.001)
					No significant increase major bleeding risk
ATTRACT[13]	Openc: efficacy and safety of pharmaco-mechanical thrombolysis to prevent PTS after proximal DVT	Pharmaco-mechanical thrombolysis + anticoagulation (337)	Anticoagulation (355)	Post-thrombotic syndrome between 6 and 24 months	No significant difference in PTS rates (47% in the pharmaco-mechanical-thrombolysis group vs. 48% in the control group; P = 0.56)
PEITHO (long-term results)[14]	Double-blind: long-term efficacy and safety of thrombolysis for intermediate-risk PE	Tenecteplase (506)	Placebo (499)	Intermediate-risk PE < 5 days and RV dysfunction and/or troponin release	Median FU 37 months:
					No significant difference in terms of mortality, residual dyspnoea, and chronic thrombo-embolic pulmonary hypertension

A, aspirin; AAA, abdominal aorta aneurysm; BES, balloon-expandable stent; CAD, coronary artery disease; CAS, carotid artery stenting; CD, clinically driven; CEA, carotid endarterectomy; CV, cardiovascular; DCB, drug-coated balloon; DES, drug-eluting stent; DVT, deep-vein thrombosis; HR, hazard-ratio; LEAD, lower-extremities artery disease; MALE, major adverse limb events; MI, myocardial infarction; PADs, peripheral arterial diseases; PTA, plain balloon angioplasty; PTS, post-thrombotic syndrome; R, rivaroxaban, R + A, rivaroxaban plus aspirin; RR, relative risk; SES, self-expandable stent; SFA, superficial femoral artery; TLR, target lesion revascularization.

[a]Defined as absence of target lesion restenosis, measured by duplex ultrasonography-derived peak systolic velocity ratio ≤ 2.5 and freedom from CD-TLR.

[b]Defined as the absence of target lesion restenosis on duplex ultrasound (peak systolic velocity ratio ≤ 2.5).

[c]With blinded assessors.

korist od empagliflozina u smanjenju smrtnosti i CV rizika (**tablica 1**), bez razlika u učestalosti amputacija u usporedbi s placebom.[6] Potreba za poboljšanom skrbi u šećernoj bolesti naglašena je u nedavnom registru s rezultatima u 15 332 bolesnika s CLTI-jem (47 % dijabetičara), koji je pokazao da se unatoč 60 % višem riziku od infekcija i 40 % višoj stopi amputacija (intrahospitalno i pri 4-godišnjem praćenju), dijabetičari revaskulariziraju rjeđe (46 % u usporedbi s 54 %, P < 0,001).[17]

U drugom preglednom članku 60 998 hospitalizacija pacijenata koji su podvrgnuti revaskularizaciji ili amputaciji u SAD-u zbog CLTI-ja, učestalost 30-dnevnog ponovnog prijma u bolnicu bila je 20 %, ponajviše zbog infekcija, perzistentnih simptoma CLTI-a, bolesti srca i proceduralnih komplikacija.[18]

Što se tiče revaskularizacije, studija ICE predstavlja prvo randomizirano istraživanje koje uspoređuje stentove koji se proširuju balonima (engl. *balloon-expandable stents*, BES) sa samoširećim stentovima (engl. *self-expandable stents,* SES)[8]. Među 660 pacijenata kojima je postavljen ilijačni stent, jednogodišnja obostrana restenoza bila je mnogo rjeđa nakon SES-a u usporedbi s BES-om (**tablica 1**). Nadalje, potreba za revaskularizacijom ciljne lezije (engl. *target lesion revascularization*, TLR) bila je više u skupini liječenoj primjenom SES-a, bez razlike u periproceduralnim komplikacijama ili funkcionalnom ishodu. Na femoropoplitealnoj razini novi dokazi vezani za odabir naprave dobiveni su iz mrežne metaanalize (6091 bolesnik).[19] Uspoređeno je pet endovaskularnih strategija: metalni stent (BMS), obloženi metalni stent (engl. *covered metal stent*, CMS), stent koji otpušta

tion and 40% higher amputation rate (both in-hospital and at 4-year follow-up), diabetic patients were revascularized less often (46% vs. 54%, *P* < 0.001).[17]

In another review of 60 998 hospitalizations of patients undergoing revascularization or amputation in the USA for CLTI, the 30-days readmission rate was 20%, mainly due to infections, persistent CLTI symptoms, cardiac conditions, and procedural complications.[18]

Regarding revascularization, the *Iliac, Common and External Artery Stent Trial* (ICE) is the first RCT to compare balloon-expandable (BES) vs. self-expandable stents (SES).[8] Among 660 patients undergoing iliac stenting, 1-year binary restenosis was significantly lower after SES as compared to BES (**Table 1**). Furthermore, freedom from target lesion revascularization (TLR) was higher in the SES group, with no difference in peri-procedural complications or functional outcome. At the femoropopliteal level, new evidence regarding device choice came from a network meta-analysis (6091 patients).[19] Five endovascular strategies were compared: bare metal stent (BMS), covered metal stent (CMS), drug-eluting stent (DES), drug-coated balloon (DCB), and plain balloon angioplasty (PTA). Drug-coated balloon, DES, and CMS offered a significant reduction in 1-year TLR vs. PTA (68%, 58%, and 48%, respectively). Additionally, DCB significantly reduced TLR also vs. BMS (53%), appearing the preferable revascularization device. The advantages of DCB were confirmed in *ISAR-STATH*, an RCT randomizing 155 patients to three different strategies:

lijek (engl. *drug eluting stent*, DES), balon obložen djelatnom tvari (eng. *drug-coated baloon*, DCB) i klasična balonska angioplastika (PTA). Balon obložen djelatnom tvari, DES i CMS pokazali su znatno sniženje jednogodišnje TLR u odnosu prema PTA (68 %, 58 % i 48 %, redom). Dodatno, DCB je doveo do znatnog sniženja TLR-a također u odnosu prema BMS-u (53 %), čineći se revaskularizacijskom strategijom izbora. Prednosti su DCB-a potvrđene u studiji ISAR-STATH, jednoj RCT u kojoj je randomizirano 155 pacijenata u trima različitim strategijama: DCB + BMS, PTA + BMS ili direkcionalna aterektomija.[9] Primarni završni ishod bio je mnogo niži za DCB + BMS nego za PTA + BMS, kao i dvogodišnja učestalost TLR-a (**tablica 1**). Daljnji dokazi u prilog DCB-a s obzirom na PTA dolaze iz studija *ILLUMENATE pivotal*[10] te *ILLUMENATE EU*[11] u kojima je randomizirano 300 u prvoj i 222 pacijenta u drugoj studiji prema DCB ili PTA: primarni stupanj otvorenosti bio je mnogo viši za DCB u objema studijama (**tablica 1**).

Kardiološki bi rizik trebao biti procijenjen u pacijenata koji se podvrgavaju vaskularnim kirurškim zahvatima.[2] U američkom nacionalnom registru bolesnika koji se podvrgavaju nekardijalnim kirurškim zahvatima, perioperativni infarkt miokarda dogodio se u 2 % pacijenata koji su podvrgnuti vaskularnim kirurškim zahvatima, što se ubraja među najviše rizike u usporedbi s ostalim vrstama nekardijalnih intervencija [odds ratio (OR) 1,56, 95 % confidence interval (95% CI) 1,52 – 1,59].[20] Putem *propensity-matched* analize rezultati iz registra upućuju na to da invazivno zbrinjavanje perioperativnog infarkta miokarda poboljšava ishod; ovo pitanje zaslužuje studiju koja će uključivati pacijente s PADs.

Bolest karotidnih arterija

OPTIMALNO MEDIKAMENTNO ZBRINJAVANJE

Pacijenti s asimptomatskom stenozom karotidne arterije trebali bi imati koristi od optimalne medikamentne terapije.[1] To je nedavno potvrđeno u 864 pacijenata s 50 – 69 %-tnom ili 70 – 99 %-tnom stenozom karotidne arterije.[21] Sveukupno, 4929 ultrazvučnih pretraga karotida provedeno je na 1439 karotidnih arterija tijekom 6,5 godina. Ishemijski moždani udar / tranzitorni ishemijski napadaj (TIA) i karotidna revaskularizacija dogodili su se u 12,2 % pacijenata, a progresija stenoze u 21,5 % pacijenata. Kvaliteta kontrole čimbenika rizika bila je neovisni prediktor za progresiju stenoze ili pojavu moždanog udara/TIA (**slika 1**).[21]

REVASKULARIZACIJA

Metaanaliza pet RCT-a, uključujući 3019 asimptomatskih pacijenata, uspoređivala je stentiranje karotidne arterije (CAS) s DCB + BMS, PTA + BMS, or directional atherectomy.[9] The primary endpoint was significantly lower for DCB + BMS than PTA + BMS, as well as 2-year TLR (**Table 1**). Further evidence favouring DCB over PTA comes from the *ILLUMENATE pivotal*[10] and *ILLUMENATE EU*[11] which randomized 300 and 222 patients, respectively, to DCB or PTA; primary patency was significantly higher for DCB in both trials (**Table 1**).

Cardiac risk should be assessed in patients undergoing vascular surgery.[2] In a nationwide US registry of patients undergoing non-cardiac surgery, peri-operative myocardial infarction occurred in 2% of patients with vascular surgery, among the highest risks compared to other types of non-cardiac intervention [odds ratio (OR) 1.56, 95% confidence interval (95% CI) 1.52–1.59].[20] Through a propensity-matched analysis, the registry suggests that invasive management of peri-operative myocardial infarction would improve outcomes; this deserves a trial enrolling patients with PADs.

Carotid artery disease

OPTIMAL MEDICAL MANAGEMENT

Patients with asymptomatic carotid artery stenosis should benefit from best medical therapy.[1] This has recently been confirmed in 864 patients with 50–69% or 70–99% carotid artery stenosis.[21] Altogether, 4929 carotid ultrasound studies were performed on 1439 carotid arteries over 6.5 years. Ischaemic stroke/transient ischemic attack (TIA) and carotid revascularization occurred in 12.2% and progression of the stenosis in 21.5% of patients. The quality of risk factors control were independent predictors for the stenosis progression or occurrence of stroke/TIA (**Figure 1**).[21]

REVASCULARIZATION

A meta-analysis of five RCTs including 3019 asymptomatic patients compared carotid artery stenting (CAS) to surgery (CEA).[5] After CAS, the risk of any peri-procedural stroke and non-disabling stroke as well as the composite of any peri-procedural stroke or death was increased with borderline statistical significance (**Table 1**). There was a trend for less peri-procedural myocardial infarctions after CAS. There was no significant difference regarding incident long-term stroke between the two techniques.

Women are at increased risk of peri-operative stroke, but gender-specific data are sparse. In the National Surgical Quality Improvement Program database (5620 CEA and 141 CAS), the early post-operative outcomes in women with sympto-

FIGURE 1. Neurologic ischaemic events and stenosis progression in patients with asymptomatic carotid stenosis according to the quality of risk factors management. Adapted from Shah *et al*.[21]

BP, blood pressure; TIA, transient ischemic attack.

kirurškim zahvatom (CEA).[5] Nakon CAS-a rizik od periproceduralnog moždanog udara i neonesposobljavajućeg moždanog udara, kao i združenog ishoda bilo kojega periproceduralnoga moždanog udara ili smrti bio je povišen uz graničnu statističku značajnost (**tablica 1**). Zapažen je trend manje učestalosti periproceduralnih infarkta miokarda nakon CAS-a. Nije bilo znatne razlike između dviju tehnika glede pojavnosti moždanih udara dugoročno.

Žene su pod povišenim rizikom od perioperativnog moždanog udara, ali su podatci specifični za spol su oskudni. Uspoređeni su rani postoperativni ishodi u žena sa simptomatskom stenozom karotidne arterije iz baze *National Surgical Quality Improvement Program* (5620 CEA i 141 CAS). Tijekom prvih 30 dana MACE se dogodio u, redom, 12,2 % i 5,2 % nakon CAS-a, odnosno CEA (P < 0,001).[22] U *propensity-matched* analizi, koja je uključivala 125 parova, 30-dnevna incidencija postoperativnog MACE-a u skupini s CAS-om bila je 11,2 % u odnosu prema 4,0 % nakon CEA (OR 2,8; P = 0,04). To ide u prilog CEA kao preferabilne opcije u žena.

Rana revaskularizacija nakon ishemijskoga moždanog udara TIA je preporučena u slučaju karotidne stenoze, ali utjecaj vremena intervencije na tehniku revaskularizacije slabo je istražen. U zajedničkoj analizi individualnih podataka 4138 pacijenata iz četiriju RCT-a rizik od moždanog udara ili smrti bio je viši nakon CAS-a nego nakon CEA u onih koji su liječeni unutar 7 dana (8,3 % prema 1,3 %, RR 6,7; 95 % CI 2,1 – 21,9, prilagođeno prema dobi, spolu i tipu kvalificirajućeg događaja).[23] Ovakvi rezultati idu u prilog CEA u ranim danima nakon neurološkoga ishemijskog događaja.

U njemačkom registru (od 2009. do 2014.) analizirano je ukupno 13 086 postupaka.[24] Intrahospitalni moždani udar ili smrt dogodili su se u 2,4 % (1,7 % asimptomatskih i 3,7 % simptomatskih pacijenata). Multivarijatna analiza pokazala je da je uporaba naprave za zaštitu od embolije neovisni prediktor nižih stopa intrahospitalnoga moždanog udara ili smrti (prilagođeni RR 0,65; 95 % CI 0,50 – 0,85), velikog moždanog udara ili smrti (prilagođeni RR 0,60; 95 % CI 0,43 – 0,84) i moždanog udara (prilagođeni RR 0,57; 95 % CI: 0,43 – 0,77). To podržava nedavne preporuke u prilog naprava za zaštitu od embolija u vrijeme CAS-a.[2]

Trenutačna praksa karotidne revaskularizacije vrednovana je u 12 zemalja.[25] Među 58 607 liječenih pacijenata, najveće nacionalne i međunarodne varijacije zapažene su u indikacijama: ukupno oko polovice pacijenata bilo asimptomatsko (48 %), ali to je variralo od 0 % (Danska) do 73 % (Italija). Nacionalna varijacija između centara bila je još i veća, i to najveća u Australiji (0 – 72 %), Mađarskoj (5 – 55 %) i u SAD-u (0 – 100 %). Vjerojatnost revaskularizacije za asimptomatsku karotidnu stenozu bila je mnogo viša u zemljama u kojima se naknada plaća operateru po slučaju (OR 5,8, 95 % CI 4,4 – 7,7). Među asimptomatskim pacijentima CAS se najčešće primjenjivao u Švedskoj (26 %), pri čemu neke zemlje (Finska, Island) nisu uopće upotrebljavale CAS. Međunarodni su napori nužni kako bi se ujednačile globalne smjernice i praksa.

Aorta

TORAKALNA AORTA

Ehokardiografija ostaje najčešća slikovna metoda za procjenu proksimalne aorte. Promjer varira ovisno o kardijalnom ciklusu, mjestu i modalitetu mjerenja, dobi i veličini tijela. U

matic carotid artery stenosis were compared. During the first 30 days, MACE occurred in 12.2% and 5.2%, respectively after CAS and CEA ($P < 0.001$).[22] In a propensity-matched analysis including 125 pairs, the 30-day incidence of post-operative MACE in the CAS group was 11.2% vs. 4.0% after CEA (OR 2.8; $P = 0.04$). This is in favour of CEA as the preferred option in women.

Early revascularization after an ischaemic stroke/TIA is recommended in case of carotid stenosis, but the influence of the timing on revascularization techniques has been poorly studied. In a pooled analysis of individual data of 4138 patients from four RCTs, the risk of stroke or death after CAS was higher than after CEA in those treated within 7 days (8.3% vs. 1.3%, RR 6.7; 95% CI 2.1–21.9, adjusted for age, sex, and type of qualifying event).[23] These results favour of CEA in the early days after a neurologic ischaemic event.

In a German registry (2009–14), a total of 13 086 CAS procedures were analysed.[24] In-hospital stroke or death occurred in 2.4% (1.7% in asymptomatic and 3.7% in symptomatic patients). The multivariable analysis showed the use of an embolic protection device was an independent predictor of lower in-hospital rates of stroke or death (adjusted RR 0.65; 95% CI 0.50–0.85), major stroke or death (adjusted RR 0.60; 95% CI 0.43–0.84), and stroke (adjusted RR 0.57; 95% CI: 0.43–0.77). This supports the recent recommendations in favour of embolic protection device during CAS.[2]

Current practice of carotid revascularization was evaluated in 12 countries.[25] Among 58 607 treated cases, the largest national and international variation was seen in indications: overall, about half of the patients were asymptomatic (48%), but this varied from 0% (Denmark) to 73% (Italy). National variation between centres was even bigger and was the highest in Australia (0–72%), Hungary (5–55%), and the USA (0–100%). The odds for revascularization for asymptomatic carotid stenosis were much higher in countries where fee per case is paid to the operator (OR 5.8, 95% CI 4.4–7.7). Among asymptomatic patients CAS was used most often in Sweden (26%) while some countries (Finland, Iceland) did not use CAS at all. An international effort is necessary to homogenize guidelines and practices globally.

Aorta

THORACIC AORTA

Echocardiography remains the most frequent imaging method to assess the proximal aorta. The diameter varies according to the cardiac cycle, site, and mode of measurement as well as age and body size. In the multicentre collaborative NORRE study including more than 700 healthy individuals, the normal reference ranges for the proximal aorta dimensions have been set.[26]

Two studies from the Multi-Ethnic Study of Atherosclerosis reported on aortic calcification on computed tomography (CT): the first assessed the ascending aorta calcium and showed that this condition is rare in general population (3.4%).[27] The ascending aorta calcium density was inversely correlated with CV events, even after adjustments for risk factors and the coronary artery calcium. The second study focused on those with coronary artery calcium score of zero and found no additional prognostic information from ascending aorta calcium.[28] A magnetic resonance imaging study showed the

multicentričnoj kolaborativnoj studiji NORRE, koja je uključivala više od 700 zdravih pojedinaca, postavljeni su normalni referentni rasponi za dimenzije proksimalne aorte.[26]

Dva istraživanja iz *Multi-Ethnic Study of Atherosclerosis* izvijestila su o aortnim kalcifikatima pri kompjutoriziranoj tomografiji (CT): prvo je procjenjivalo kalcij ascendentne aorte i utvrdilo da je ovakvo stanje rijetko u općoj populaciji (3,4 %).[27] Gustoća kalcija ascendentne aorte obrnuto je korelirala s CV događajima, čak i nakon prilagodbe prema čimbenicima rizika i prema kalciju koronarnih arterija. Drugo je istraživanje bilo usredotočeno na one s vrijednošću kalcijskog skora 0 i nisu registrirani dodatni prognostički parametri na temelju kalcija ascendentne aorte.[28] Studija oslikavanja primjenom magnetne rezonancije pokazala je prognostički interes u brzini pulsnog vala aortnog luka, koji je marker aortne krutosti u ispitanika srednje životne dobi (45 – 54 godine), ali ne i u starijih dobnih skupina.[29]

Glede aortnih događaja, za sada se samo aortni promjer smatra markerom rizika za aortnu disekciju dobivenim primjenom slikovnih metoda. Dvije neovisne *case-control* studije, koje su uspoređivale pacijente s aortnom disekcijom tipa B (TB-AD) s kontrolnim ispitanicima, pokazale su da je, uz promjer aorte, elongacija aortnog luka povezana s dobi također u vezi s povišenim rizikom od TB-AD-a.[30,31]

ABDOMINALNA AORTA

Nakon probira, male AAA zahtijevaju praćenje promjera, tipično 2D ultrazvukom (US). Uporaba 3D-US za procjenu volumena AAA u 179 pacijenata s malim AAA pokazala je da 3D-US precizno procjenjuje i promjer i volumen u usporedbi s CT-om.[32] Tijekom razdoblja praćenja 40 % bolesnika koji su bili klasificirani kao stabilni prema promjeru, zapravo su pokazali povećanje volumena, što pak ističe veću osjetljivost ove, nove metode.

Podatci iz jednog od najiscrpnijih nacionalnih registara u Europi dolaze iz Finske i pokazuju poboljšanje prognoze pacijenata s nerupturiranim i rupturiranim AAA tijekom posljednja 2 desetljeća (**slika 2**).[33] Mreža *VascuNet* analizirala je razlike u intervencijskim metodama AAA i ishodima u 83 252 pacijenta u 11 zemalja tijekom razdoblja od 2005. do 2009. i 2010. do 2013. godine.[34] Udio osamdesetogodišnjaka koji su operirani između tih dvaju razdoblja porastao je s 18,5 % na 23,1 % (P < 0,0001) i slično se povećao udio pacijenata liječenih endovaskularnom korekcijom aneurizme (EVAR) s 44,3 % na 60,6 % (P < 0,0001). Smrtnost se kod EVAR-a smanjila se s 1,5

prognostic interest of the aortic arch pulse-wave velocity, a marker of aortic stiffness, in middle-age (45–54 years) subjects, but not at older ages.[29]

Regarding aortic events, so far only the aortic diameter is considered as a risk marker from imaging for aortic dissection. Two independent case-control studies, comparing patients with type-B aortic dissection (TB-AD) with controls, suggest that beyond the diameter, the age-related elongation of the aortic arch is also associated with increased risk of TB-AD.[30,31]

ABDOMINAL AORTA

After screening, small AAAs require follow-up of the diameter, typically assessed by 2D ultrasound (US). Using 3D-US for assessment of AAA volume in 179 patients with small AAAs, it was found that 3D-US was accurate in assessing both diameter and volume as compared to CT.[32] During follow-up, 40% patients classified as stable according to the diameter actually presented a volume growth highlighting the higher sensitivity of this new method.

Data from one of the most comprehensive and nationwide registries in Europe come from Finland, showing the improvement in the prognosis of patients with unruptured and ruptured AAA during the last 2 decades (**Figure 2**).[33] The VascuNet network analysed differences in AAA interventional methods and outcomes in 83 253 patients through 11 countries during the 2005–09 and 2010–13 periods.[34] The proportion of octogenarians operated increased between the two periods from 18.5% to 23.1% ($P < 0.0001$) and similarly the proportion of patients treated with endovascular aneurysm repair (EVAR) increased from 44.3% to 60.6% ($P < 0.0001$). Mortality for EVAR decreased from 1.5% to 1.1% ($P < 0.0001$), but the outcome worsened for open repair from 3.9% to 4.4% ($P = 0.008$).

In some countries, AAAs are repaired by EVAR at a lower diameter than recommended in guidelines. Based on data from almost 40 000 Medicare patients undergoing EVAR from 2001 to 2008, earlier AAA repair by 5 mm has major consequences, with 22% excess EVAR procedures and 42% and 37% increase in open and endovascular re-interventions.[35] The cost per saved AAA rupture was estimated to be 1 million USD.

After EVAR lifelong surveillance is necessary and CT-angiography has been the preferred modality, while ultrasound duplex scanning (DUS) with and without contrast enhancement (CEUS) is an alternative. A Cochrane review of 42 studies[36] concluded that both DUS and CEUS a have high speci-

FIGURE 2. Management of abdominal aorta aneurysm in the nationwide registry in Finland, 2000–14. Adapted from Laine *et al*.[33]

AAA, abdominal aorta aneurysm; EVAR, endovascular aneurysm repair.

% na 1,1 % (P < 0,0001), ali se ishod za otvorenu korekciju pogoršao s 3,9 % na 4,4 % (P=0.008).

U nekim zemljama AAA su korigirane putem EVAR-a pri nižemu promjeru od onoga koji je preporučen u smjernicama. Na temelju podataka od gotovo 40 000 pacijenata iz sustava *Medicare* koji su podvrgnuti EVAR-u u razdoblju od 2001. do 2008., ranija korekcija AAA za 5 mm ima znatne posljedice, uz 22 % suvišnih postupaka te 42 %, odnosno 37 % porasta otvorenih i endovaskularnih reintervencija.[35] Cijena po spašenoj rupturi AAA procjenjuje se na oko 1 milijun američkih dolara.

Nakon EVAR-a doživotno je praćenje nužno, pri čemu je CT angiografija bila preferirani modalitet, dok je oslikanje dupleks ultrazvukom (DUS) s primjenom kontrasta (CEUS) i bez njega jedna od alternativa. Cochrane pregled 42 studije[36] zaključio je da i DUS i CEUS imaju visoku specifičnost u utvrđivanju *endoleaka*; međutim, CEUS je osjetljiviji i može se primjenjivati rutinski, a CT snimanje samo kada se sumnja na *endoleak*.

Venska tromboembolija

Nakon akutne epizode venske tromboembolije (VTE), antikoagulantna terapija indicirana je tijekom najmanje tri mjeseca.[37] Optimalno je trajanje antikoagulantnog liječenje, duljeg od početnog razdoblja, neizvjesno. Prandoni *i sur.* pokazali su da antikoagulantna terapija u bolesnika s prvom epizodom proksimalne DVT, temeljena na procjeni ostatne venske tromboze i serijskog praćenja D-dimerom, dovodi do ukupne godišnje stope recidiva VTE <5 %.[38] Međutim, u muškaraca ova strategija zahtijeva dodatno vrednovanje. Predloženo je nekoliko predikcijskih pravila kako bi se utvrdili pacijenti koji su pod visokim rizikom od recidiva.[39] Studija REVERSE II prospektivno je validirala kliničko predikcijsko pravilo *„men continue and HERDOO2"*.[40] Ono omogućuje utvrđivanje žena s niskim rizikom nakon prve neprovocirane VTE, koje mogu na siguran način prekinuti antikoagulantno liječenje nakon što se završi početno liječenje (3,0 %-tni recidiv po pacijentu na godinu u žena niskog rizika). Nisu nađeni prediktori niskog rizika za recidiv u muškaraca. Odluku o tome prekinuti ili ne prekinuti antikoagulantnu terapiju treba donijeti individualno i s obzirom na rizik od krvarenja.

Kada se jednom donese odluka o produljenju antikoagulantnog liječenja, uvriježeno je da se nastavi s inicijalnim lijekom. Posljednja studija EINSTEIN-CHOICE[12] dokazala je da standardna (20 mg jednom na dan) i niska doza rivaroksabana (10 mg jednom na dan) znatno snizuje rizik od recidiva u usporedbi s ASK-om, bez znatnog porasta učestalosti krvarenja (**tablica 1**).

U pacijenata s proksimalnom DVT na terapiji DOAC-om, perzistencija rezidualne venske tromboze rjeđa je nego u bolesnika na konvencionalnoj antikoagulantnoj terapiji. Ovi rezultati mogu imati implikacije za prognozu pacijenata s DVT-om.[41]

Prema trenutačnim smjernicama, adjuvantna kateterom navođena tromboliza može se razmotriti u pojedinih bolesnika s akutnom iliofemoralnom DVT ako se provodi u iskusnim centrima kako bi se smanjio rizik od posttrombotskog sindroma (PTS). Međutim, nedavno objavljena studija ATTRACT (692 bolesnika) nije dokazala dobrobit od kateterom navođene trombolize u smanjenju PTS-a, ali je utvrdila veći rizik od velikih krvarenja.[13] Premda je indeks težine PTS-a bio niži u farmakomehaničkoj skupini, to nije utjecalo na kvalitetu života pacijenata. Nije bilo razlike ovisno o lokalizaciji DVT-a (57 % je imalo iliofemoralnu DVT). Ukupni su rezultati kontradiktorni

ficity for identification of endoleaks; however, CEUS is more sensitive and can be routinely used, with CT scan only when endoleak is suspected.

Venous thromboembolism

After an acute episode of venous thromboembolism (VTE) anticoagulation is indicated for at least 3 months.[37] Optimal anticoagulation duration, beyond the initial period remains uncertain. Prandoni *et al.* showed that anticoagulation in patients with a first episode of proximal DVT, based on the assessment of residual vein thrombosis and serial D-dimer, leads to an overall annual rate of recurrent VTE <5%.[38] However, in men this strategy needs further assessment. Several prediction rules are proposed to identify patients at high risk of recurrence.[39] The REVERSE II study prospectively validated the 'men continue and HERDOO2' clinical prediction rule.[40] This allows identifying low-risk women, following a first unprovoked VTE, who can safely discontinue anticoagulation once the initial treatment is completed (3.0% recurrence per patient-year in low-risk women). No predictors for low risk of recurrence were found in men. The decision on whether to discontinue anticoagulation should therefore be individually tailored and balanced against bleeding risk.

Once the decision to extend anticoagulant treatment is taken, common agreement is to continue with the initial compound. The latest EINSTEIN-CHOICE trial[12] showed that standard (20 mg o.d.) and lower dose rivaroxaban (10 mg o.d.), significantly reduced the risk of recurrence compared to aspirin, without significant increase in bleeding rates (**Table 1**).

In patients with proximal DVT treated with DOACs, persistence of residual vein thrombosis is likely to occur less frequently than in patients treated with conventional anticoagulation. These results may have implications for the prognosis of patients with DVT.[41]

According to current guidelines, adjuvant catheter-directed thrombolysis may be considered in selected patients with acute ilio-femoral DVT, if performed in experienced centres, to diminish risk of post-thrombotic syndrome (PTS). However, the recently published ATTRACT trial (692 patients) failed to show the additional interest of catheter-directed thrombolysis to decrease the risk of PTS, but did result in a higher risk of major bleeding.[13] While the PTS severity score was lower in the pharmacomechanical group, this did not affect improve the quality of life of the patients. There was no difference according to the site of DVT (57% had ilio-femoral DVT). The overall results are in contradiction with a smaller trial reported previously in favour of pharmacomechanical intervention, with decreased risk of PTS after 5 years of follow-up.[42] Further trials, focused on ilio-femoral DVT, are required.

The clinical usefulness of VTE risk prediction scores in ambulatory cancer patients is debated. A cohort of 876 cancer patients compared several scores (**Table 2**).[43] All models performed poorly (c-statistics: 0.50–0.57), indicating the need for improvements before these models can be considered in clinical practice. Identifying predictors for VTE recurrence in cancer patients remains a challenge. In two cohorts of patients with cancer-associated VTE, the modified Ottawa score showed modest discriminating power and was unable to predict the risk of VTE recurrences.[44,45]

TABLE 2. Characteristics included in the risk prediction scores for cancer-related venous thromboembolism (VTE).

	Khorana	Vienna CATS	PROTECHT	CONKO
Very high-risk tumours (pancreatic or gastric cancer)[a]	2	2	2	2
High-risk tumours (lung, gynaecological, lymphoma, bladder, or testicular cancer)	1	1	1	1
Pre-chemotherapy haemoglobin <10 g/dL or use of erythropoietin stimulating agents	1	1	1	1
Pre-chemotherapy white blood cell count >11 × 10^9/L	1	1	1	1
Pre-chemotherapy platelet count ≥350 × 10^9/L	1	1	1	1
Body mass index >35 kg/m^2	1	1	1	
D-dimer >1.44 µg/mL		1		
Soluble P-selectin ≥53.1 ng/mL		1		
World Health Organization (WHO) performance status ≥2				1
Gemcitabine chemotherapy			1	
Platinum-based chemotherapy			1	
Cut-off for classification of high-risk patients (points)	≥3	≥5	≥3	≥3

Numbers represent the value attributed to each characteristic in the scores.

[a]The Vienna CATS also included brain cancer as a high-risk site.

u odnosu prema manjoj studiji koja je prethodno objavljena i išla je u prilog farmakomehaničkoj intervenciji, s nižim rizikom za PTS nakon 5 godina praćenja.[42] Potrebne su dodatne studije s fokusom na iliofemoralnu DVT.

Klinička korist od bodovne predikcije rizika od VTE-a u ambulantnih pacijenata s malignim bolestima predmet je rasprave. Kohorta od 876 pacijenata s malignim tumorima uspoređivala je nekoliko bodovnih sustava (**tablica 2**).[43] Svi su modeli imali loš rezultat (c-statistika: 0,50 – 0,57), upozoravajući na potrebu poboljšanja bodovnih sustava prije negoli se ti modeli mogu razmatrati u kliničkoj praksi. Utvrđivanje prediktora recidiva VTE-a u pacijenata s malignim tumorima i dalje je izazov. U dvjema kohortama pacijenata s VTE povezanom s malignim tumorima modificirani Ottawa bodovni sustav pokazao je skromnu moć razlučivanja i nije omogućivao predviđanje rizika od recidiva VTE-a.[44,45]

Dijagnostički se algoritmi učestalo upotrebljavaju za identifikaciju pacijenata u kojih se plućna embolija (PE) može isključiti bez uporabe CT angiografije plućnih arterija (CTPA). U studiji kod 3465 bolesnika sa sumnjom na PE pravilo odluke YEARS (koje se temelji na trima kliničkim čimbenicima kombiniranima s dvostrukom razinom D-dimera) dovelo je do 14

Diagnostic algorithms are frequently used to identify patients in whom pulmonary embolism (PE) can be ruled out without the use of computed tomography pulmonary angiography (CTPA). In a study of 3465 patients with suspected PE, the YEARS decision rule (based on three clinical items combined with two D-dimer cut-offs) yielded a 14% decrease in CTPA examinations compared to conventional strategies (**Figure 3**) with a negative predictive value of 99.4%.[46] Whether negative CTPA is sufficient to exclude PE in patients with likely pretest probability is debated. Pulmonary embolism was excluded with CTPA in 37% of patients with likely clinical probability, and the 3-month VTE risk was 0.6%, indicating that a negative CTPA safely excludes PE in this patient group.[47]

The prevalence of PE in patients presenting with syncope has been highly debated this year, following the PESIT trial, reported last year,[39] describing a 17% rate of PE in syncope cases referred to emergency rooms, after excluding cases with evident aetiology. A meta-analysis including 6608 emergency department patients and 975 patients hospitalized for syncope reported a PE prevalence <1%.[48] Two other studies reported a PE prevalence of 1.4% among patients with synco-

FIGURE 3. The YEARS diagnostic strategy in case of suspicion for pulmonary embolism.

CTPA, computed tomography pulmonary angiography; DVT, deep vein thrombosis; PE, pulmonary embolism.

%-tnog sniženja broja CTPA pretraga u usporedbi s uobičajenim strategijama (**slika 3**) s negativnom prediktivnom vrijednosti od 99,4 %.[46] Predmet je rasprave je li negativna CTPA dostatna za isključenje PE-a u bolesnika koji imaju visoku vjerojatnost za PE prije pretrage. Plućna embolija isključena je pomoću CTPA u 37 % pacijenata s visokom kliničkom vjerojatnosti, a tromjesečni rizik za VTE bio je 0,6%, pokazujući da negativna CTPA s velikom sigurnošću isključuje PE u toj skupini bolesnika.[47]

Prevalencija PE-a u pacijenata u kojih se očituje sinkopa bila je veliki predmet rasprave ove godine, prema prošlogodišnjoj objavi studije PESIT[39], koja je opisala 17 %-tnu učestalost PE-a u slučajevima sinkope koji su otpušteni iz hitne službe, nakon što je isključena moguća etiologija. Metaanaliza koja je uključivala 6608 pacijenata iz hitnih službi i 975 pacijenata hospitaliziranih zbog sinkope, utvrdila je prevalenciju PE <1 %.[48] Dvije druge studije izvijestile su o prevalenciji PE od 1,4 % među bolesnicima sa sinkopom.[14,49] Rutinski probir za PE u svih bolesnika u kojih se očituje sinkopa vjerojatno nije opravdan.

Studija PEITHO istraživala je dugoročnu prognozu u bolesnika sa srednjorizičnom PE randomiziranih na trombolizu ili placebo.[50] Trombolitička terapija nije smanjila stopu dugoročne smrtnosti, perzistentne zaduhe, kronične tromboembolijske plućne hipertenzije ili disfunkcije desne klijetke.

pe.[14,49] Routine screening for PE in all patients presenting with syncope may not be justified.

The PEITHO trial investigated long-term prognosis in patients with intermediate-risk PE randomized to receive thrombolysis or placebo.[50] Thrombolytic treatment did not decrease long-term mortality rates, persisting dyspnoea, chronic thromboembolic pulmonary hypertension, or right ventricular dysfunction.

Conflict of interest: V.A.: AstraZeneca, Bayer, Boehringer-Ingelheim, Novartis, Pfizer/BMS Alliance, Sanofi. S.B.: none. L.M.: Bayer, Pfizer/BMS Alliance, Sanofi. H.S.: Amgen, Bayer, Novo Nordisk, B Braun, Philips and Cook Medical. M.V.: Bayer. M. De C.: Daiichi-Sankyo, Abbott Vascular, Philips-Volcano, Sanofi.

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