LÉKAŘSKÁ FAKULTA V PLZNI

UNIVERZITA KARLOVA V PRAZE

ÚROVEŇ SEKUNDÁRNÍ PREVENCE A PROGNÓZA PACIENTŮ PO ISCHEMICKÉ CÉVNÍ MOZKOVÉ PŘÍHODĚ

SECONDARY PREVENTION PRACTICE AND PROGNOSIS OF PATIENTS AFTER ISCHEMIC STROKE

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Disertační práce

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Disertační práce doktorandského studia

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ABSTRAKT

Ischemická cévní mozková příhoda (iCMP) je jednou z nejčastějších příčin invalidity a mortality v celosvětovém měřítku a sekundární prevence, která je postavená na obdobných základech jako u ischemické choroby srdeční (ICHS), dokáže být účinným nástrojem vedoucím ke snížení rekurence iCMP i celkové mortality. Zatímco v sekundární prevenci ICHS je již delší dobu stanoven pevný systém dispenzarizace pacienta s důrazem na komplexní ovlivnění rizikových faktorů, v oblasti sekundární prevence iCMP není adekvátní péče zatím plně implementována do reálné praxe. Cílem naší práce bylo komplexní zhodnocení současného stavu sekundární prevence u pacientů po iCMP, její srovnání s populací s ICHS a analýza některých nekonvenčních rizikových faktorů. V českém souboru mezinárodních multicentrických průzkumů projektu EUROASPIRE Stroke Modul či Stroke Survey zahrnujících pacienty po iCMP vyšetřené v roce 2007 až 2013 jsme zjistili, že v iniciální fázi došlo k významnému zvýšení podílu pacientů, kteří byli přijati ke specializované neurologické léčbě na iktovou jednotku, včetně zvýšení počtu podání systémové fibrinolýzy. V sekundární péči však není situace zdaleka tak příznivá. Kontrola hypertenze, jednoho z nejvýznamnějších rizikových faktorů iCMP vůbec, není lepší než u hypertoniků v obecné populaci. Navzdory patrnému příznivému trendu pouze velmi malá skupina pacientů dosahuje doporučených cílových hodnot LDL cholesterolu, nemalá část pacientů s fibrilací síní neužívá pro ně tak esenciální antikoagulační terapii. Stále mezi pacienty po iCMP persistuje rozsáhlá skupina pacientů závislých na tabáku. Skutečným klinickým problémem je extrémní, neklesající prevalence poruchy glukózového metabolismu. Více než 50% pacientů po iCMP má poruchu glukózové tolerance či manifestní diabetes. Též dispenzarizace většiny pacientů není vedena kompetentním specialistou. Ve srovnání s korespondujícím vzorkem pacientů s manifestní ICHS je u pacientů po iCMP patrná horší kontrola všech rizikových faktorů. Prokázali jsme také o 85% vyšší riziko celkové mortality či o 89% vyšší riziko kardiovaskulární mortality v populaci pacientů po iCMP ve srovnání s pacienty s manifestní ICHS i po plné adjustaci faktorů. Při testování dalších potenciálních morbiditních a mortalitních činitelů byl nalezen paradoxní vztah mezi nadváhou a zlepšenou prognózou. V podskupině pacientů s nedeterminovaným subtypem iCMP se ukázala být významně riziková kombinace kuřáctví s polymorfizmem genu pro protrombin. Jako společný mortalitní činitel iCMP a ICHS byla identifikována zvýšená hladina desfosforylované nekarboxylované MGP. Ke komplexnímu zhodnocení psychosociálních dopadů iCMP se ukázala být užitečná dotazníková monitorace pomocí SF 36, dle které lze identifikovat jedince s vyšší mortalitní zátěží. V závěru práce jsou diskutovány připadné změny a budoucí trendy, které by mohly vést ke zkvalitnění sekundární prevence v této relativně opomíjené populaci.

Kličová slova: ischemická cévní mozková příhoda, ischemická choroba srdeční, sekundární prevence, EUROASPIRE, ESH-Stroke Survey, rizikové faktory, hypertenze, dyslipidemie, kuřáctví, prothrombin, dp-ucMGP, SF 36 score.

ABSTRACT

It is evident that cerebrovascular disease including ischemic stroke belongs to the most common cause of disability or death in the world population. Secondary prevention in poststroke patiens can lead to reduce risk of recurrence or extend lifetime like in coronary heart disease (CHD). The principles of secondary prevention are well implemented in population with CHD, but the situation in poststroke patients is quite different. The assesment of secondary prevention in poststroke patiens and a comparison with patient with CHD was selected for a goal of this study. The study population consisted of Czech patients examined in the framework of well-defined surveys in patients after their first ischemic stroke. Patients represented pooled Czech samples of the project EUROASPIRE Stroke Modul or Stroke Survey in 2007 and in 2013. Better results in acute care were detected. Admissions in stroke unit in 2013 were realized more often than 2007 and fibrinolisis was aplicated more frequently too. On the contrary, arterial hypertension wasn´t controlled better than the general population of hypertonics. Despite the decrease of average lipid level, patients didn´t reach the target values in general. Also many poststroke patients couldn´t quit smoking. There was a big group of postsroke patients without anticoagulation therapy. The real problem is a high prevalency of disorders of glucose metabolism, more than 50 percent patients had impaired glucose tolerance or diabetes mellitus. In the next part, we compared the adherence to secondary prevention principles between poststroke and CHD patients. Stroke was associated with a significant 85% risk of increase of all-cause mortality and 89% risk of increase of cardiovascular mortality. Poststroke patients were significantly less frequently treated with antiplatelets or anticoagulants, all antihypertensive and lipid-lowering drugs. Furthemore, we analysed less frequent factors of stroke. This study showed a „paradox“ interaction between overweight and better life expectancy in poststroke patients. There was also detected that mortality after undetermined subgroup of stroke in smokers with polymorphism gene of prothrombin was higher than in other subgroup of stroke. Another result was the finding that icreased level of dp-ucMGP was associated with higher cardiovascular and total mortality in patiens with stable aterovascular disease including stroke. The key for identifying the patients after stroke with independent psychosocial mortality risk is regular using a questionnaire SF 36 or HADS score. At the end, we are considering medical trends, guidelines and future in secondary prevention of stroke.

Key words: ischemic stroke, coronary heart disease, secondary prevention, EUROASPIRE, ESH-Stroke Survey, risk factors, hypertension, dyslipidemia, smoking, prothrombin, dp-ucMGP, SF 36 score.

SEZNAM POUŽITÝCH ZKRATEK

ACE angiotensin converting enzym

ADP adenosine diphosphate **(**receptor)

ASA acetylsalycilic acid

ARB angiotensin receptor brocker

BMI body mass index

CAS carotid artery stenting

CCS Causative Classification of Stroke Systém

CEA carotid thrombendarterectomy

CEPT cholesterylester transfer protein

CI confidence interval

CMP cévní mozková příhoda

CT computer tomography

ČR Česká republika

DAPT dual antiplatelet terapy

DPP 4 dipeptidyl peptidase 4

MGP Matrix Gla protein

ESH European society of hypertension

EKG elektrokardiogram

FiS fibrilace síní

FN fakultní nemocnice

GLP-1 glucagon like peptide 1 (receptor)

HADS Hospital Anxiety And Depression Scale

HbA1C glykovaný hemoglobin

HDL high density lipoprotein

HR hazard ratio

iCMP ischemická cévní mozková příhoda

ICHS ischemická choroba srdeční

IM infarkt myokardu

INR International Normalized Ratio

LDL low density lipoprotein

LoE level of evidence

MACE major adverse cardiac events

NOAC new oral anticoagulans

oGTT oral glucose tolerance test

OR odds ratio

PCSK9 proprotein convertase subtilisin/kexin 9

QoL quality of live

RF rizikový faktor

RR risk ratio

SD standard deviation

SF36 short form 36 (score)

SGLT2 sodium/glukose cotransporter 2

STK systolický krevní tlak

TK krevní tlak

TG triacylglycerol

TIA tranzitorní ischemická ataka

USA Spojené státy americké

WHO světová zdravotnická organizace

I. ÚVOD DO PROBLEMATIKY

1. HISTORIE EPIDEMIOLOGIE A PREVENCE ATEROVASKULÁRNÍCH CHOROB

Kardiovaskulární choroby představují v celosvětovém měřítku dlouhodobě nejčastější příčinu úmrtí a ateroskleróza tepenného systému zároveň největší „neinfekční“ pandemii všech dob. Nejčastější formou aterovaskulární choroby zůstává ve většině populací (včetně evropské) ischemická choroba srdeční (ICHS), což ale neznamená, že aterosklerotické postižení v jiných lokalizacích nepředstavuje zásadní zdravotně-sociální a ekonomický problém. Je evidentní, že cerebrovaskulární choroby, a to zejména ischemické cévní mozkové příhody (CMP), můžeme co do epidemiologického významu postavit mezi kardiovaskulárními chorobami hned na pomyslné druhé místo, zatímco z hlediska individuálního dopadu na postiženého pacienta mohou CMP představovat daleko závažnější medicínský i sociální problém než nejobvyklejší manifestace aterovaskulární choroby, tj. infarkt myokardu (neboť filozoficky řečeno, mozek je právě to, co z nás dělá lidské bytosti). První náznaky epidemie aterovaskulárních chorob byly poprvé zaznamenány již ve 20. letech 20. století v USA. Do popředí zájmu se ale aterovaskulární choroby dostaly až po II. světové válce, kdy zvyšující se počet nemocných vedl již k založení celého oboru kardiovaskulární epidemiologie. V roce 1948 americký National Heart Institute inicioval první velkou epidemiologickou, dnes již legendární Framinghamskou studii, která také poprvé objektivizovala kauzalitu čtyř základních rizikových faktorů (RF) v patofyziologii aterovaskulárních chorob, tj. hypertenzi, dyslipidémii, kouření a poruchy glukózového metabolismu. Epidemie aterovaskulárních chorob se týká prakticky všech populací, a to nejen v rozvinutých průmyslových zemích Severní Ameriky a Evropy, ale i v rozvojových zemích (jakkoliv se relativní impakt jednotlivých faktorů mezi populacemi může dosti zásadně lišit). Výskyt aterovaskulárních chorob progredoval ještě do poloviny šedesátých let, ale v průběhu sedmdesátých let je již s jistotou potvrzen opačný trend, tj. pokles mortality na aterovaskulární choroby, opět nejprve v USA a posléze i v západní Evropě. Bohužel odlišný vývoj jsme mohli pozorovat v České

republice, kde kardiovaskulární i celková mortalita stoupaly přinejmenším do druhé poloviny osmdesátých let a kde jednoznačný a doposud trvající pokles v těchto parametrech jsme s jistotou mohli potvrdit až po politické změně v roce 1989. Je třeba také zmínit, že Česká republika byla první ze zemí bývalého sovětského bloku, kde byl tento pokles zaznamenán, a právě zásadní pokles v kardiovaskulární mortalitě zůstává dodnes nepochybným „motorem" prodlužování průměrného věku naší populace [1]. Pokud se zaměříme pouze na cerebrovaskulární choroby, jejich trend v podstatě dlouhodobě kopíruje vývoj mortality na ICHS. K poklesu počtu cerebrovaskulárních chorob došlo jen o něco málo dříve (cca 1-2 roky), nejspíše v důsledku poměrně zásadního rozvoje antihypertenzní léčby v průběhu 80. let. Relativní „příspěvek" cerebrovaskulárních chorob ke globální kardiovaskulární mortalitě zůstává u mužů zhruba poloviční, než je tomu v případě ICHS. U žen se mortalita mezi oběma hlavními skupinami aterovaskulárních chorob liší spíše jen marginálně, to je ale dáno pravděpodobně především obecně daleko nižším rizikem ICHS u žen. Konkrétnější epidemiologické údaje k této problematice je možno dohledat např. ve Zprávě o zdraví obyvatel České republiky z roku 2014 (http://www.mzcr.cz). Obor preventivní kardiologie pochází z konce 60. let 20. století a u jeho zrodu stáli především britský epidemiolog Goefrey Rose a jeho američtí současníci Henry Blackburn, Jeremiah Stamler a jeho manželka Rose. V bývalém Československu je nutno zmínit jako jednoho z nestorů profesora Zdeňka Reiniše, ale bezesporu mezi ně patří také zakladatel plzeňského pracoviště a vlastně celé školy profesor Jaroslav Šimon. Pokud se zaměříme na praktickou realizaci opatření v kardiovaskulární prevenci (primární i sekundární), asi nejzásadnějším přelomem byla publikace prvních Společných doporučení evropských odborných společností pro prevenci kardiovaskulárních chorob (tzv. první „Task force") z roku 1994 [2]. Tato doporučení se tak spolu se svými následnými revizemi [2-7] stala obrazně řečeno „biblí" preventivní kardiologie a asi nejcitovanějším zdrojem z této oblasti vůbec.

2. RIZIKOVÉ FAKTORY CEREBROVASKULÁRNÍCH CHOROB A MOŽNOSTI JEJICH INTERVENCE

Díky společnému etiologickému základu cerebrovaskulární choroby jistě sdílejí téže RF s dalšími formami aterovaskulární choroby (tedy zejména ICHS). Na druhé straně je nutno konstatovat, že relativní vliv jednotlivých faktorů je v některých případech odlišný a do etiologie CMP dosti zásadně vstupují i další parametry, zejména z tromboembolické oblasti. Následující text shrnuje hlavní komponenty rizika CMP, a to se zaměřením na ty, kde máme k dispozici alespoň teoretickou možnost jejich terapeutického ovlivnění a na něž je tedy cíleně zaměřena péče v sekundární prevenci cerebrovaskulárních chorob.

2.1 Arteriální hypertenze

Arteriální hypertenze je velmi pravděpodobně tím nejvýznamnějším ovlivnitelným rizikovým faktorem v sekundární prevenci ischemické cévní mozkové příhody[8], přičemž je definována obyvklým způsobem jako hodnota systolického tlaku ≥ 140 mm Hg a/nebo diastolického tlaku ≥ 90 mmHg, která byla naměřena opakovaně alespoň při dvou různých návštěvách lékaře [9] (či již chronicky užívaná antihypertenzní léčba). Arteriální hypertenze patří také mezi nejčastější RF v obecné populaci vůbec – v ČR s prevalencí kolem 40% [10]. Nicméně u pacientů po ischemické CMP je prevalence arteriální hypertenze samozřejmě daleko vyšší a dosahuje přibližně 70% [11]. Riziko vzniku ischemické CMP je přímo úměrné výši krevního tlaku a jeho vliv lze sledovat již při hodnotách systolického tlaku začínajících na 115 mmHg [12,13]. Studie PATS (Post-Stroke Antihypertensive Treatment Study), publikovaná v roce 1995, byla první významná studie potvrzující benefit léčby hypertenze u pacientů po proběhlé ischemické cévní mozkové příhodě [14]. Do této studie bylo randomizováno 5665 pacientů po recentně proběhlé cévní mozkové příhodě (ischemické či hemorhagické) či transitorní ischemické atace (TIA) a srovnáván byl efekt indapamidu oproti placebu. Po uplynutí 24 měsíců byl pozorován pokles TK ve větvi léčené placebem o 6.7 mmHg a ve větvi léčené

indapamidem 12,4 mmHg. Podávání indapamidu bylo po 30 měsících sledování spojeno se signifikantním poklesem rizika rekurence mozkové příhody, 44,1% při podávání placeba a 30,9% u pacientů léčených indapamidem [relative risk (RR), 0.3 (95% intervaly spolehlivosti (CI): 0.14–0.43)]. Další významnou prospektivní klinickou studií, která prokázala snížení rizika recidivy cerebrovaskulární příhody u pacientů léčených antihypertenzní farmakoterapií byla studie PROGRESS (Perindopril Protection Against Recurrent Stroke Study) [15]. Do této studie bylo zahrnuto 6105 pacientů po proběhlé TIA a ischemické či hemorhagické cévní mozkové příhodě. Pacienti byli rozděleni do aktivně léčené skupiny a skupiny léčené placebem. Na základě individuálního rozhodnutí lékaře byla terapie dále doplněna o indapamid (nebo placebo) dle designu dvojitě zaslepené studie. Iniciální hodnoty krevního tlaku nebyly vstupním kritériem pro zařazení do studie a asi 35% pacientů nebylo v době zařazení do studie léčeno antihypertenzivy a mělo hodnoty krevního tlaku nižší než 160/95 mmHg. Tato část sledované populace zahrnovala normotenzní pacienty, ale též jedince s arteriální hypertenzí I. stupně dle WHO (systolický krevní tlak 140-159mmHg / diastolický krevní tlak 90-99 mmHg). Po čtyřech letech sledování byl u aktivně léčené skupiny pacientů ve srovnání s placebem sledován průměrný pokles krevního tlaku o 9/4 mmHg a statisticky významný pokles relativního rizika recidivy mozkové příhody o 28% (95% CI: 17% - 38%). Při srovnání podskupiny léčené kombinační léčbou perindopril s indapamidem s placebem pokles hodnot krevního tlaku dosahoval dokonce 12.3/5 mmHg a byl spojen s poklesem relativního rizika o 48% [(95% CI: 0.30- 0.54)]. Samotná monoterapie perindoprilem snižovala krevní tlak o 5/3 mmHg a nevedla ke statisticky významnému poklesu počtu příhod [15]. V následujících letech byla autory studie PROGRESS provedena post hoc analýza, která studovala skupiny pacientů dle hodnot systolického krevního tlaku (≥160, 140-159, 120-139 a < 120mmHg) a prokázala, že efekt antihypertenzní terapie na rekurenci mozkových příhod klesá přímo úměrně s poklesem hodnot systolického krevního tlaku (RR 39%, 31%, 14% a

0%) při srovnatelné účinnosti antihypertenzní léčby. U pacientů s dosaženými nižšími hodnotami systolického krevního tlaku nebyl sledován významnější vzestup nežádoucích účinků terapie ani nárůst mozkových příhod. Srovnání antihypertenzní terapie a placeba zkoumala také meta-analýza čínských autorů zahrnující 10 randomizovaných studií z roku 2009[16]. Ta opět zahrnovala pacienty po proběhlé TIA a ischemické i hemorhagické mozkové příhodě s dobou sledování od 2 do 5 let. Bylo potvrzeno, že antihypertenzní terapie vede ke snížení rekurence mozkových příhod (RR, 0.78, 95% CI: 0.68-0.90). Efekt byl pozorován u diuretik (či kombinace diuretika s ACE inhibitory). U ostatních lékových skupin v monoterapii, zahrnující též monoterapii ACE inhibitory, signifikantní pokles rekurence mozkových příhod pozorován nebyl, nicméně zdroj dat pro hodnocení jednotlivých látek, zejména betablokátorů a blokátorů kalciových kanálů, byl omezený. Při srovnávání účinnosti jednotlivých skupin antihypertenziv v sekundární prevenci cerebrovaskulárních příhod se můžeme opřít také o randomizovanou studii MOSES (Morbidity and Mortality after Stroke, Eprosartan Compared with Nitredipin for Secondary Prevention)[17]. Do této studie bylo zařazeno celkem 1405 jedinců s anamnézou proběhlé TIA nebo ischemické či hemorhagické cévní mozkové příhody. Pacienti byli rozděleni do dvou skupin. Jedna skupina byla léčena nitredipinem a druhá skupina byla léčena eprosartanem. Jedinci léčení eprosartanem vykazovali menší riziko cerebrovaskulárních příhod (incidence density ratio 0.75, 95% CI: 0.57-0.97), které bylo dáno převážně poklesem TIA, avšak ve výskytu ischemických či hemorhagických mozkových příhod významný rozdíl mezi těmito látkami nebyl. Eprosartan dále prokázal lepší efektivitu v primárním kompozitním endpointu (smrt, kardiovaskulární či cerebrovaskulární příhoda [incidence density ratio 0.79 (95% CI, 0.66-0.96)].

Za nepřímé ukazatele prospěšnosti snižování krevního tlaku u pacientů po cerebrovaskulární příhodě lze považovat i výsledky meta-analýz, které byly zaměřeny na hypertoniky v primární prevenci. Rozsáhlá meta-analýza více než 40 randomizovaných prací prokázala, že léčba

arteriální hypertenze vede k 30 – 40% poklesu rizika vzniku cerebrovaskulární příhody, přičemž benefit terapie narůstá s intenzitou snižování krevního tlaku [13]. Je ovšem nutné podotknout, že u části ze zařazených studií byla arteriální hypertenze definována hodnotou krevního tlaku ≥ 160/100 mmHg (dle mezinárodně uznávané definice hypertenzní choroby se jedná již o hypertenzi II. a III. st.).

Aktuálně platná doporučení Evropské hypertenzní společnosti z roku 2013 [18] pro léčbu hypertenze v rámci primární kardiovaskulární prevence doporučují zahájení farmakoterapie při hodnotách krevního tlaku 140/90-159/99 mmHg (hypertenze I. st.) u pacientů s vysokým kardiovaskulárním rizikem (s gradingem doporučení I.). U pacientů s hypertenzí I. st. a nízkým a středním kardiovaskulárním rizikem by farmakoterapie měla být zvážena po několika týdnech až měsících sledování při selhání režimových opatření (IIa). Cílové hodnoty farmakoterapie hypertenze jsou stanoveny na obvyklých 140/90 mmHg, i když u diabetiků se zdají být prospěšnější naopak cílové hodnoty diastolického tlaku nižší než 85 mmHg a u pacientů starších 65 let naopak benevolentnější hodnota 150/90 mmHg. Doporučené postupy České hypertenzní společnosti v podstatě kopírují doporučení evropská s výjimkou cílových hodnot krevního tlaku u diabetiků, kde je doporučována přísnější kontrola krevního tlaku s hodnotami ≥ 130/80 mmHg [9]. Aktuálně platná doporučení Americké hypertenzní i kardiologické společnosti uvádějí zahájení farmakoterapie v primární prevenci u všech dospělých pacientů s hypertenzní chorobou I. st [19]. U pacientů starších 60 let je strategie zahájení léčby i cílových hodnot volnější a doporučuje se zahájení antihypertenzní terapie až při krevním tlaku ≥ 150/90 mmHg (a tato hodnota je taktéž cílem léčby).

Na tomto místě je ale třeba zdůraznit, že cílová hodnota léčby není uzavřenou otázkou. V posledních letech proběhlo několik klinických studií, které naznačují, že ideální cílové hodnoty krevního tlaku u pacientů po cévní mozkové příhodě by mohly být i nižší než aktuálně akceptovaná hranice 140/90 mmHg. Studie ACCORD [20] zkoumala efekt

intenzivní kontroly krevního tlaku u diabetiků II. typu s vysokým kardiovaskulárním rizikem. U části pacientů byla aplikována přísná kontrola systolického krevního tlaku s hodnotami < 120 mmHg. U druhé poloviny pacientů byl stanoven cílový systolický krevní tlak < 140 mmHg. V primárním kompozitním endpointu (nefatální infarkt myokardu, nefatální ischemický iktus a smrt z kardiovaskulární příčiny) nebyl mezi skupinami pozorován statisticky významný rozdíl. Nicméně samotný fatální i nefatální iktus se u pacientů s přísnější kontrolou krevního tlaku vyskytoval významně méně [fatální iktus: hazard ratio (HR), 0.59; 95% CI: 0.39 - 0.89; p=0.01 a nefatální iktus: HR 0.63; 95% CI: 0.41 - 0.96; P=0.03). Studie SPS3 (Secondary Prevention of Small Subcortical Strokes) [21] opět srovnávala efekt intenzivnější a volnější kontroly krevního tlaku, avšak v populaci pacientů s lakunárním iktem (pacienti s jiným typem ischemického iktu byli vyřazeni). Zahrnovala celkem 3020 pacientů, u kterých byla diagnóza potvrzena magnetickou rezonancí. Pacienti byli rozděleni do skupin s cílovým systolickým tlakem < 150 mmHg a s cílovým systolickým tlakem < 130 mmHg. Po 12 měsících sledování nebyl zaznamenán statisticky významný rozdíl v kompozitním endpointu (HR 0.84, 95% CI: 0.68 – 1.04) ani v počtu recidiv ischemické cévní mozkové příhody (HR 0.84, 95% CI: 0.66 – 1.09). Ve skupině s intenzivnější kontrolou krevního tlaku byl prokázán statisticky významně nižší výskyt pouze u izolovaných hemorhagických mozkových příhod.

Problematika hypertenze v akutní fázi ischemické mozkové příhody je podrobněji rozebrána v kapitole 3.1 a vychází z doporučených postupů americké hypertenzní společnosti „Guidelines for the Early Management of Patients With Acute Ischemic Stroke“ z roku 2013 [22]. Ve světle těchto doporučení lze konstatovat, že aktivní snižování krevního tlaku v prvních 24 hodinách je doporučeno pouze při hodnotách >220/120 mmHg. V případě indikace podání systémové trombolýzy jsou ale nezbytné hodnoty krevního tlaku <180/105 mmHg. Obnovení antihypertenzní terapie u hypertoniků léčených již před mozkovou

příhodou je možné po uplynutí 24 hodin za podmínky plné neurologické stability. Nové zavedení antihypertenzní terapie se doporučuje při přetrvávání hodnot krevního tlaku ≥140/90 mmHg s odstupem několika dní.

Význam nefarmakologických léčebných postupů a úpravy životního stylu, který je u hypertoniků všeobecně doporučován, nebyl u pacientů po proběhlé cévní mozkové příhodě podrobněji zkoumán (ale o jejich přínosu celkem není nutno pochybovat).

Souhrn v současné době platných doporučení pro léčbu arteriální hypertenze u pacientů po ischemické CMP či TIA udává následující tabulka [8]:

Zahájení léčby krevního tlaku je doporučeno u pacientů s iCMP nebo TIA, u nichž byl po několika dnech prokázán krevní tlak ≥ 140/90 mmHg	I; *LoE B*
Přínos zahájení léčby u pacientů s krevním tlakem ≤ 140/90 mmHg není jistý.	IIb; *LoE C*
Obnovení antihypertenzní léčby u pacientů se známou a léčenou arteriální hypertenzí je doporučeno po několika dnech od manifestace iCMP nebo TIA.	I, *LoE A*
Cílové hodnoty krevního tlaku nejsou přesně známy, je vhodné dosáhnout krevního tlaku < 140/90 mmHg.	IIb; *LoE B*
U pacientů s proběhlou iCMP lakunárního typu se zdá být vhodné dosáhnout systolického krevního tlaku < 130 mmHg.	IIa; *LoE C*
Optimální lékový režim není znám, diuretika a kombinace diuretik s ACEI jsou dle dostupných vědeckých poznatků prospěšná.	I, *LoE A*
Úprava životosprávy je vhodná součást komplexní antihypertenzní léčby.	IIa; *LoE B*

pozn: levý sloupec udává třídu (grading) doporučení a *sílu důkazu (LoE, Level of Evidence)*

2.2. Dyslipidemie

Jakkoliv je etiologický význam poruch lipidového metabolismu v případě cerebrovaskulárních chorob menší, než je v případě ICHS, stále patří mezi velmi významné RF ischemické CMP i TIA. Lipidový metabolismus je modifikován vnitřními, genetickými faktory, ale z velké míry též nevhodnými stravovacími návyky v podobě vysoké konzumace živočišných tuků, kaloricky bohatých potravin či nadměrného přísunu alkoholu, dále také absencí adekvátního energetického výdeje. Dle výsledků populačního šetření studie postMONICA z roku 2009 trpí až 81% mužů a 70.6 % žen poruchou lipidového metabolismu [10]. Také vrozené formy dyslipidémií jsou v populaci poměrně hojně zastoupeny, prevalence familiární hypercholesterolémie v heterozygotní formě je minimálně 1:200 jedinců populace. Mortalitní benefit snižování hladiny LDL cholesterolu byl prokázán u pacientů s ICHS v mnoha rozsáhlých kontrolovaných studiích [23] a dle dostupných důkazů se jeví pokles rizika vaskulární choroby jako lineární a přímo úměrný hodnotě LDL cholesterolu (na základě této skutečnosti dochází k průběžnému snižování cílových hodnot LDL cholesterolu zejména u pacientů s manifestní kardio- či cerebrovaskulární chorobou). Aktuální doporučení Evropské kardiologické společnosti z roku 2016 stanovuje cílového hodnoty LDL cholesterolu u velmi rizikových pacientů < 1.8 mmol/l [7], a je dosti pravděpodobné, že ani tato hranice není definitivní. Agresivní snižování LDL cholesterolu a jeho efekt na morbiditu a mortalitu pacientů po ischemické CMP či TIA byl sledován ve studii SPARCL [24]. Do této studie bylo zahrnuto 4731 pacientů s hodnotami LDL cholesterolu 5.6 – 10.5 mmmol/l (100 – 190 mg/dL). Polovině pacientů byl podáván atorvastatin v dávce 80 mg denně a druhé polovině pacientů bylo podáváno placebo. Po celkové době sledování 4,9 let bylo prokázáno absolutní snížení rizika recidivy ischemické CMP o 2,2% ve prospěch léčby atorvastatinem [HR 0.84, 95% CI: 0.71–0.99; P=0.03] a absolutní snížení rizika velké kardiovaskulární příhody o 3.3% opět ve prospěch aktivně léčených pacientů (HR, 0.80; 95% CI: 0.69–0.92;

P=0.002). Tento pozitivní mortalitní efekt byl sledován nezávisle na věku, pohlaví či na typu cévní mozkové příhody. Při analýze nežádoucích účinků léčby měli pacienti atorvastatinem vyšší hodnoty jaterních a svalových enzymů, ale bez signifikantního nárůstu jaterního selhání či rhabdomyolýzy. Určitým nepříjemným překvapením byl pouze signifikantní nárůst incidence hemorhagické mozkové příhody (n=55 [2.3%] u statinem léčených pacientů versus n=33 [1.4%] v placebové větvi).

Mimo neoddiskutovatelné role LDL cholesterolu se v etiopatogenezi uplatňují také změny hladiny triacylglycerolu a HDL cholesterolu. Zvýšená hladina triacylglycerolu je asociována s ischemickými ikty, které jsou spojené s onemocněním velkých tepen. Nízké hodnoty HDL cholesterolu a vysoké hodnoty lipoproteinu se zdají být asociovány se zvýšeným rizikem ischemického iktu. Výsledky velkých meta-analýz naznačují, že niacin a fibráty by mohly mít pozitivní efekt na morbiditu a možná i mortalitu u pacientů po CMP, nicméně interpretace těchto výsledků je diskutabilní, zejména proto, že všechny tyto studie proběhly v době před zavedením statinů do léčby a převážně zkoumaly populace v primární prevenci. Přidání niacinu k léčbě statiny u pacientů s manifestním aterosklerotickým onemocněním a aterogenní dyslipidemií (nízkou hladinou HDL společně s vysokou hladinou triacyglycerolů a vysokou hladinou malých denzních LDL částic) zkoumala studie AIM-HIGH (Atherothrombosis Intervention in Metabolic Syndrome With Low HDL/High Triglycerides: Impact on Global Health Outcomes Trial). [25] Část pacientů byla léčena kombinací atorvastatinu 40-80mg s 1500-2000 mg niacinu denně a druhá skupina pouze monoterapií atorvastatinu ve stejné dávce. Studie byla po třech letech sledování zastavena pro absenci klinického efektu kombinační léčby navzdory sledovanému poklesu triglyceridů, LDL cholesterolu a vzestupu HDL. Překvapivým výsledkem byl naopak patrný nárůst incidence primárních ischemických iktů ve skupině léčené niacinem ve srovnání s placebem (27[1.6%] versus 15 pacientů [0.9%]) a tento trend byl nesignifikantně naznačen i v celém sledovaném

souboru včetně pacientů v sekundární prevenci po ischemickém iktu. Nelze jednoznačně stanovit, zda se jedná o náhodný jev nebo o příčinnou souvislost, ale niacin je také spojen s poměrně četnými nežádoucími účinky v podobě záchvatovitého „flushe“. Studie HPS-2 THRIVE, která srovnávala pacienty, jejichž léčba byla doplněna o niacin s laropiprantem. Bohužel také neprokázala účinnost niacinu v prevenci aterovaskulárních příhod, přidání laropiprantu vedlo pouze ke snížení nežádoucích účinků niacinu. Celkově se tato cesta ukázala tedy být spíše „slepou uličkou“.

Neúspěchem též skončilo testování inhibitorů CEPT (torce- , dalce-, anace- a evacetrapib), které dle laboratorních testování svým účinkem výrazně zvyšují hladiny HDL. Podávání těchto léků navzdory vzestupu HDL nevedlo k signifikantnímu snížení mortality ani počtu aterotrombotických příhod (naopak např. torcetrapib byl spojen s významným vzestupem krevního tlaku).

Slibnější směr představuje kombinační léčba s ezetimibem, kde ve velké (a extrémně dlouhé) studii IMPROVE-IT kombinace ezetimibu 10 mg se středně dávkovaným statinem (40-80mg simvastatinu) vykazovala signifikantně vyšší redukci sledovaných kardiovaskulárních endpointů [26]. Jakkoliv tato studie nebyla primárně realizována u pacientů s cerebrovaskulární chorobou, lze její výsledky do určité míry tímto směrem interpretovat.

Velkým příslibem pro budoucnost hypolipidemické terapie jsou inhibitory PCSK9, jejichž účinnost v sekundární prevenci byla recentně prokázána ve studie FOURIER [27]. Podrobnější data týkající se jejich širšího využití v sekundární prevenci cerebrovaskulárních chorob zatím nejsou k dispozici.

Základní principy léčby dyslipidémie v sekundární prevenci u pacientů po ischemické CMP či TIA, tak jak jsou formulovány v platných Doporučeních, [8] jsou uvedeny v následující tabulce. Tato Doporučení, na rozdíl od společných evropských Guidelines, [7] vysloveně neformulují cílovou hodnotu LDL, kterou bychom měli léčbou dosáhnout.

Léčba statinem je doporučena u všech pacientů po ischemické mozkové příhodě s předpokládanou aterotrombotickou etiologií při hodnotě LDL cholesterolu ≥ 2,6 mmol/l (100 mg/dL) s anamnézou ale i bez anamnézy jiného manifestního aterosklerotického onemocnění.	I; *LoE B*
Intenzivní hypolipidemická léčba statiny* je doporučena u pacientů po ischemické mozkové příhodě s předpokládanou aterotrombotickou etiologií i při hodnotě LDL cholesterolu < 2,6 mmol/l (100 mg/dL) i bez anamnézy jiného manifestního aterosklerotického onemocnění.	I; *LoE C*
Léčba dyslipidemie u pacientů po iCMP nebo TIA ve spojení s dalšími aterosklerotickými komorbiditami by měla být souladu s doporučením ostatních odborných společností pro léčbu dyslipidémií doplněna o modifikaci životního stylu, fyzické aktivity a dietní opatření.	I; *LoE A*

* s dosaženým poklesem LDL o 50%

2.3 Porucha glukozového metabolismu

Poruchy glukózového metabolismu můžeme didakticky rozdělit na diabetes mellitus I. typu, poruchu glukózové tolerance a diabetes mellitus II. typu. Všechny tyto klinické jednotky jsou definovány nadhraničními až významně elevovanými hodnotami lačné či postprandiální glykémie nebo zvýšenými hodnotami glykovaného hemoglobinu. Porucha glukozové tolerance je definována lačnou glykémií ≤ 7,0 mmol/l a glykémií ve druhé hodině orálního glukózového tolerančního testu (oGTT) 7,0 – 11,0 mmol/l. Za manifestní diabetes jsou považovány hodnoty lačné glykémie > 7,0 mmol/l nebo glykémií v druhé hodině oGTT > 11,0 mmol/l nebo hodnoty glykovaného hemoglobinu ≥ 48 mmol/mol. Kromě toho má prognostický význam již i tzv. porušená glykemie nalačno, obyvkle definovaná jako lačná glykemie ≥ 5.6 mmol/l. [28] Prevalence diabetu II. typu je vysoká a navíc roste celosvětově. V evropské populaci ve věku 20 – 71 let má asi 8% diabetes mellitus II. typu a daších více než 9% poruchu glukózové tolerance. Výskyt tohoto onemocnění navzdory všem preventivně léčebným opatřením trvale narůstá a do roku 2030 se anticipuje nárůst až o 20% [29]. Etiopatogeneze poruchy glukózové tolerance až rozvoje diabetu mellitu II. typu je multifaktoriální. Nadměrný kalorický příjem, obezita (až 90% diabetiků II. typu trpí obezitou), fyzická inaktivita vedou u predisponovaných jedinců k nadměrné produkci

mastných kyselin a cytokinu v tukové tkáni. Na podkladě těchto působků dochází k rozvoji inzulinové rezistence v ostatních tkáních, hyperinzulinémii, k rozvoji aterogenní dyslipidemie a posléze i ke zvýšeným hladinám glykémie v séru. Spojovacím mostem mezi diabetem a aterosklerozou se zdá být zejména aktivace makrofágů, které se ve formě pěnových buněk ukládají v cévní stěně a vedou k rozvoji tukových proužků až kompaktních aterosklerotických plátů. Zánětlivá a cytokinová reakce je také základním mechanismem rozvoje endoteliální dysfunkce s poškozováním intimy jak malých, tak velkých cév. Diabetes mellitus je prokázaným rizikovým faktorem ischemické cévní mozkové příhody. Diabetici mají 1.5 – 3.7 krát vyšší riziko rozvoje ischemického iktu a více než 8.4% mozkových příhod je přímo spojeno s diabetem II. typu. Prevalence poruchy glukózové tolerance u pacientů po TIA nebo CMP je minimálně 28%, četnost diabetu je však ještě vyšší a pohybuje se mezi 25 – 40%. [30] V podskupině prospektivní Cardiovascular Health Study, která sledovala pacienty po první ischemické cévní mozkové příhodě, byl diabetes mellitus spojen s 60% vzestupem rizika recidivy iktu (RR, 1.59; 95% CI: 1.07–2.37) [31] .

Efekt léčebné intervence diabetu či poruchy glukózové tolerance u pacientů v sekundární prevenci ischemické cévní mozkové příhody zatím nebyl systematicky zkoumán a doporučení vycházejí spíše ze studií, které byly cílené na smíšené populace. Je známo, že farmakoterapií a změnou životního stylu lze docílit oddálení rozvoje diabetu u pacientů s poruchou glukózové tolerance. Změna životního stylu u pacientů s poruchou glukózové tolerance vedla ke snížení incidence rozvoje diabetu mellitu o 60% ve srovnání s placebem [32]. Podávání metforminu snižovalo incidenci o 31% a podávání askarbózy vedlo k podobnému snížení incidence jako metformin, avšak bylo doprovázeno významně vyšším počtem nežádoucích gastrointestinálních účinků [32]. V prevenci cerebrovaskulárních příhod u diabetiků byly také zkoumány thiazolidindiony, které svým účinkem zvyšují citlivost periferních tkání na inzulin. Výsledky mortalitních studií však prokázaly spíše opačný efekt těchto látek, který byl spojený

s nárůstem hmotnosti a zvýšeným rizikem kardiovaskulárních příhod (a pyoglitazon dokonce významně zvyšoval riziko rozvoje karcinomu močového měchýře). [33] Z výše uvedených důvodů byly thiazolidindiony shledány jako rizikové a v populaci s vysokým rizikem kardio- a cerebrovaskulárních příhod nejsou obecně doporučovány.

Poměrně novou lékovou skupinou mezi antidiabetiky jsou glutiny (inhibitory dipeptidylpeptidázy 4, DPP-4). Zatím všechny dokončené studie u těchto nadějných preparátů, které příznivě ovlivňují glykémii a snižují úroveň glykovaného hemoglobinu, a to vše bez rizika hypoglykémií, neprokázaly snížení kardiovaskulárního rizika ani celkové mortality [34]. Saxogliptin ve studii SAVOR-TIMI53 (Saxagliptin and Cardiovascular Outcomes in Patients with Type 2 Diabetes Mellitus) dokonce statisticky významně zvyšoval riziko hospitalizace pro srdeční selhání [35].

Perorální antidiabetikum, u kterého se dokázal příznivý vliv na kardiovaskulární mortalitu včetně snížení rizika srdečního selhání, je empagliflosin. Mechanismus účinku tohoto léku spočívá v inhibici sodíko-glukózového kotransportéru (SGLT2) s navozením glykosurie a poklesu glykémie v séru. Studie EMPA-REG OUTCOME (Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes) prokázala statisticky významný pokles kardiovaskulární mortality o 38 % (HR = 0,62; 95% CI: 0,49–0,77) a statisticky významné snížení relativního rizika nového rozvoje srdečního selhání o 37%. Užívání empagliflozinu také vedlo k poklesu hodnot systolického krevního tlaku průměrně o 4 mmHg [36]. Při podrobnějším rozboru výsledků však nedošlo k poklesu nefatálních infarktů myokardu a výskyt nefatálních ischemických iktů byl nesignifikantně zvýšen o 24 % (HR = 1,24; 95% CI: 0,92–1,67; p = 0,16) ve srovnání s placebem. Větší část mozkových příhod však byla pozorována u pacientů v době déle než 30 dní po přerušení léčby, přičemž v době aktivní léčby byla v obou větvích prakticky stejná. Lze se tedy domnívat, že léčba empagliflozinem

sice nevede ke snížení počtu příhod, ale tyto příhody nebyly tak závažné jako u pacientů v placebové větvi [36].

Přiznivý profil z hlediska redukce kardiovaskulárních příhod vykazovalo ve studii LEADER (Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes) také jiné novější antidiabetikum, a to liraglutid (analog GLP-1, glucagon-like propeptide-1). [37]

Léčebné cíle u diabetiků po proběhlé ischemické CMP a TIA se spíše než o hodnoty aktuálních glykémií a glykemických profilů opírají o hladinu glykovaného hemoglobinu. Není založena na cílové hodnotě, jak je tomu u ostatních parametrů, ale používá pojem „maximální bezpečné cílové hodnoty“, tj. glykovaný hemoglobin okolo 48 mmol/mol. [7,8]

Léčba k nižším hodnotám glykovaného hemoglobinu (cca mezi 40-42 mmol/L) již byla spojena se zvýšenou mortalitou s ohledem na riziko hypoglykemie a s ní související kardiovaskulární kompromitací (zejména s rizikem maligních arytmií). [38,39] „Těsná“ kompenzace diabetu je dle doporučení diabetologických společností určena pouze pro úzkou skupinu mladých pacientů s dlouhým životním výhledem, bez rozvinutých kardiovaskulárních komplikací a s nízkou frekvencí hypoglykémií. U starších, polymorbidních pacientů s frekvenčními hypoglykémiemi má být volena spíše volná kompenzace diabetu (cílové hodnoty 53 – 63 mmol/mol). [8]

Na základě výše uvedených poznatků je v sekundární prevenci iCMP a TIA všeobecně doporučována komplexní terapie s důrazem na změnu životního stylu, podávání metforminu, dobré kontroly krevního tlaku s cílovými hodnotami ≤ 130/80 mmHg (což je doporučení i České hypertenzní společnosti [9]) a intezivní léčbu statinem.

.Základní principy intervence poruchy glukozového metabolismu v sekundární prevenci cerebrovaskulárních chorob podle platných Doporučení [8], shrnuje opět následující tabulka:

Pacienti po proběhlé ischemické CMP nebo TIA byl měli podstoupit diagnostiku zaměřenou na průkaz poruchy glukózové tolerance provedením náběru lačné glykémie, orálního glukózového tolerančního testu nebo stanovením glykovaného hemoglobinu. Hodnoty glykémie mohou být v akutním stádiu iCMP nebo TIA zkreslené. Stanovení glykovaného hemoglobinu je přesné i v časné době po proběhlé příhodě.	IIa; *LoE C*
U pacientů po proběhlé ischemické CMP nebo TIA s prokázanou poruchou glukózové tolerance či diabetem je doporučena antidiabetická léčba i komplexní intervence kardiovaskulárních rizik dle aktuálních doporučení diabetologických společností.	I; *LoE B*

2.4 Kouření a konzumace alkoholu

Kouření je neoddiskutovatelně jedním ze zcela zásadních RF všech forem aterovaskulární choroby, včetně chorob cerebrovaskulárních. Prevalence kuřáctví zejména v rozvojových zemích a zemích východního bloku je vysoká až extremní (v některých zemích, což neplatí o České republice, dokonce ještě narůstá). U nás bylo v populaci jedinců starších 15 let dle údajů českého statistického úřadu z roku 2015 celkem 24,1% kuřáků (27,3% mužů a 21,1% žen). Počet kuřáků v posledních dvou desetiletích přece jenom klesá (31,3% versus 24,1%), ale především zásluhou mužů, naopak prevalence kouření mezi ženami se významněji nemění [40]. Alarmující je též přetrvávající vysoká prevalence kuřáků ve věku 15 – 24 let (35,3%), která patří mezi nejvyšší v Evropě (blíže viz Zpráva o zdraví obyvatel České republiky z roku 2014 http://www.mzcr.cz). Kouření v populaci pacientů staršího věku po proběhlé CMP nebo TIA je spojeno s dvojnásobným rizikem rekurence příhody (HR, 2.06; 95% CI, 1.39–3.56) [31]. Vliv pasivního kouření na rekurenci mozkové příhody nebyl dostatečně zkoumán.

Odvykání kouření, zejména pod vedením specializovaného centra s využitím všech dostupných nefarmakologických i farmakologických postupů, je jednou ze základních metod vedoucích ke snížení rizika celkové i kardiovaskulární mortality. Meta-analýza 12 porspektivních studií Wilsona a kolegů prokázala, že ukončení kouření po infarktu myokardu je spojeno s asi 61% poklesem mortality [41]. Jakkoliv nemáme k dispozici data o přínosu

ukončení kouření u pacientů po CMP, není žádný důvod se domnívat, že nebude přínos podobný jako v případě pacienetů s ICHS. Na druhé straně, jen asi 4% kuřáků dokáží bez odborné pomoci dlouhodobě přestat kouřit a u zbytku této populace perzistuje závislost na tabáku dlouhodobě. Kombinovaná intervence ve specializovaných poradnách, zahrnující náhradní nikotinovou léčbu a další farmaka, dokáže úspěšnost po prvním roce léčby zvýšit až na necelých 40%, nicméně dlouhodobá abstinence je opět poměrně zásadně nižší [42].

Často se hovoří o přínosu mírné konzumace alkoholu z hlediska redukce kardiovaskulárního rizika. Obecně v sekundární prevenci vaskulárních chorob toto nikdy nebylo spolehlivě potvrzeno (a dle našich vlastních dat je efekt v nejlepším případě neutrální). Naopak, pravidelná konzumace většího množství alkoholu, zejména v podobě nárazových alkoholových excesů, riziko recidivy iktu zvyšují. V případě hemorhagické CMP stoupá riziko spojené s příjmem alkoholu v podstatě lineárně [43,44]. Nelze pominout ani ostatní nepříznivé efekty dlouhodobé konzumace alkoholu, jako je vysoké riziko vzniku závislosti, fibrilace síní, ethylické kardiomyopatie či diabetu mellitu [45,46]. Doporučení pro sekundární prevenci po CMP a TIA z roku 2014 shledává denní příjem alkoholu u mužů do 40 g a u žen do 20 g jako přijatelný [8], nicméně aktuálnější Guidelines pro prevenci kardiovaskulárních chorob jsou již přísnější a doporučují denní příjem alkoholu u mužů do maximálně 20g, resp. u žen pouze do 10g denně [7]. V každém případě, mírnou spotřebu alkoholu můžeme vždy maximálně tolerovat, a nikdy ne doporučovat jako prostředek ke snížení kardiovaskulárního rizika.

Souhrnně tyto principy pro cerebrovaskulární choroby udává opět následující tabulka [8]:

Každému pacientovi po iCMP a TIA má být přísně doporučeno zanechat kouření.	I; *LoE C*
Je vhodné, aby se pacienti po iCMP a TIA vyhýbali pasivní expozici tabákového kouře.	IIa; *LoE B*
Specializované poradenství, substituce nikotinu a další farmakoterapie odvykání kouření jsou účinnými nástroji, které mohou pomoci s abstinencí od kouření.	I; *LoE A*
Pacienti po proběhlé ischemické CMP, hemorhagické CMP nebo TIA, kteří jsou více než mírnými konzumenty alkoholu, by měli spotřebu eliminovat či alespoň redukovat.	I; *LoE C*
Mírná spotřeba alkoholu na úrovni 2 drinků u mužů či 1 drinku u žen je akceptovatelná, ale abstinentům by v žádném případě nemělo být doporučováno takto alkohol konzumovat.	IIb; *LoE B*

2.5 Fibrilace síní

Fibrilace síní (FiS) sama o sobě nepatří mezi konvenční faktory aterovaskulární choroby, ale speciálně u ischemické CMP hraje naopak jednu z klíčových etiologických rolí. Z opačného pohledu právě kardioembolizační CMP představuje nejzásadnější komplikaci FiS (která by jinak představovala v podstatě benigní arytmii). Odhaduje se, že FiS je zodpovědná za 10-12% všech ischemických CMP, což jenom v USA představuje více než 70 000 nových případů ročně [47] (či více než 1.5 milionu případů celosvětově). Hlediska relativního rizika incidence CMP zvyšuje přítomnost FiS asi 5x. FiS je více prevalentní u mužů a stoupá exponenciálně s věkem. Ve skupině do 60 let je prevalence méně než 1%, zatímco po 80. roce u mužů již více než 10%. [48]

Zcela zásadní změnu v osudu pacientů s FiS přinesly studie dokazující přínos antikoagulační léčby (warfarinu) v prevenci CMP. Meta-analýza těchto studií zahrnující více než 28 000 pacientů s non-valvulární FiS prokázala v souhrnu, že léčba warfarinem byla spojena s 64% redukcí rizika CMP [49]. Na druhou stranu, roční incidence mrtvice stoupá exponenciálně s každým bodem skórovacího systemu CHADS (s faktorem vždy 1.5x vstupní hodnota), což

dává roční incidenci CMP u pacientů s nejvyšším CHADS skóre více než 8%. [50] Lze tedy říci, že ponechat pacienta s FiS bez antikoagulační léčby (pokud k tomu není zásadnější medicínský důvod) se rovná jeho těžkému poškození a závažnému medicínskému pochybení. Na druhé straně warfarin přes svůj nesporný přínos není ani z daleka ideálním antikoagulans. Především jeho terapeutické okno je velmi úzké a z hlediska antikoagulačního účinku jakékoliv vychýlení z rozmezí INR 2-3 vede k významnému vzestupu rizika buď směrem k vyšší incidenci ischemických CMP, resp. vyššímu výskytu krvácivých komplikací (včetně hemorhagických CMP) [51,52]. Navíc oba typy těchto komplikací mají (podobně jako FiS) významný věkově podmíněný vzestup, což v součtu vede k situaci, kde velké množství pacientů s FiS ve vyšším věku antikoagulační léčbu neužívá z celkem opodstatněných obav z nežádoucího účinku (prudký pokles indikace warfarinu je pozorován u pacientů již od 75. roku věku) [53]. Druhým obvyklým problémem léčby warfarinem je, že i mezi těmi léčenými zůstává poměrně zásadní část mimo náležité rozmezí INR (tj. 2-3). V naprosté většině provedených analýz nebyla proporce pacientů setrvávající v náležitém rozmezí INR vyšší než 60%. Tedy 40% pacientů mělo špatnou compliance k léčbě a hodnoty INR mimo terapeutické rozmezí, což vedlo k zásadnímu narůstu rizika CMP (u nejméně kompliatních až trojnásobně) [54]. Zlepšení v tomto směru by mohla přinést extenzivnější preskribce tzv. „nových antikoagulancií“ (NOAC). Ta zasahují do koagulace odlišným mechanismem než warfarin (přímou inhibicí buď faktoru Xa nebo IIa), ale především nevyžadují monitoraci účinku a jejich dávkování je podstatě jednotné. Studie s NOAC (a v indikaci FiS máme nyní k dispozici 4 zástupce této skupiny) vesměs prokázaly přinejmenším podobnou (ale někdy i vyšší) antikoagulační ochranu než warfarin, ale i přiznivější bezpečnostní profil (a maximum přínosu v tomto směru je tvořeno poklesem rizika hemorhagických iktů) [55].

Souhrnná doporučení [8] ohledně FiS udává opět následující tabulka:

Jak warfarin, tak NOAC jsou indikovány u všech pacientů s nevalvulární FiS (permamentní i paroxysmální forma).	I; *LoE A*
Pacienty léčené warfarinem je třeba udržovat v terapeutickém rozmezí s cílem INR 2.5 (v rozmezí 2-3).	I; *LoE A*
U pacientů, kteří prodělali CMP či TIA bez jiné zřetelné etiologické přičiny, je vhodné prolongované sledování (holterizace) s hlediska přítomnosti možné FiS.	IIa; *LoE C*
Kombinace antikoagulační a antiagregační léčby není obecně doporučována, ale je přijatelná v případě akutního koronárního syndromu s implantací stentu.	IIb; *LoE C*
Pacienty s vyslovenou kontraindikací antikoagulační léčby (warfarin nebo NOAC) mohou užívat aspirin. Přínosná může být duální antiagregace s clopidogrelem.	IIb; *LoE B*
Pro většinu pacientů s FiS po ischemické CMP by měla být antikogualační léčba zahájena již v prvních 14 dnech. Pouze v případě vyššího rizika hemorhagické konverze ischemického ložiska (velké léze, hemorhagická transformace na iniciálním zobrazení, nekontrolovaná hypertenze…) je vhodné toto zahájení odložit.	IIa, *LoE B*
U pacientů po CMP či TIA, kde je nutno antikoagulační léčbu z jakéhokoliv důvodu přerušit, je přemosťující terapie nízkomolekulárním heparinem přijatelnou alternativou.	IIa; *LoE C*

2.6. Stenoza arteria carotis

Stenotické postižení velkých tepen lze identifikovat jako základní příčinu úmrtí přibližně u 20% ze všech proběhlých ischemických mozkových příhod. Velké množství klinických studií srovnávalo nejen rozdíly mezi konzervativní a revaskularizační léčbou, ale také jednotlivé techniky revaskularizace u populací pacientů různého věku, pohlaví, přidružených komorbidit, dále také načasování revaskularizačního výkonu a dlouhodobé výsledky v závislosti na rozsahu stenózy karotické tepny. Výsledky tří významných ramdomizovaných studií ECST (European Carotid Surgery Trial), NASCET (North American Symptomatic Carotid Endarterectomy Trial) a VACS (Veterans Affairs Cooperative Study Program) jednoznačně prokazují redukci recidivy ipsilaterální iCMP v následující pěti letech u pacientů se symptomatickou stenózou a karotis interna s redukcí lumen > 70% dle neinvazivních vyšetřovacích metod léčených karotickou endarterektomií (CEA) a naopak absenci jakéhokoliv benefitu z revaskularizace při redukci lumen < 50%. [56-58] Šedou zónou je tedy

u symptomatické stenózy rozsah obstrukce lumen 50-69%. Studie NASCET [57] v této skupině pacientů prokazuje hraniční trend v poklesu četnosti recidiv iktů u pacientů léčených CEA oproti konzervativní terapii (15.7% vs 22.2%, p=0.045), který byl závislý na profilu pacienta (věk, pohlaví, komorbidity) a mimo jiné také na zkušenosti operatéra. Hranice operačního rizika určující zachovaný benefit z CEA (perioperační iCMP nebo smrt) ve srovnání s konzervativním postupem byla v této studii < 6.7%. Jedním z důležitých faktorů přinášejících benefit z revaskularizace je také její načasování. Dle subanalýzy tří výše uvedených studií byla největší redukce primárního endpointu (recidiva iktu nebo smrt do 30 dnů po primární CMP) pozorována u pacientů operovaných do 2 týdnů po příhodě (30%), méně již u pacientů operovaných v době mezi 2.-4. týdnem (18%) a nejméně u operovaných v období mezi 4.-12. týdnem. Po 2-3 letech je riziko i u pacientů s významnou (>70%) stenózou stejné jako u pacientů asymptomatických a není zde tedy indikace k revaskularizaci [59]. Kontroverzní je negativní vliv pohlaví na peroperační morbiditu a dlouhodobé výsledky revaskularizace. V subanalýze studie NASCET zaměřené na rozdíly dle pohlaví vykazovaly ženy statisticky horší průběh revaskularizace i časnější reokluzi ošetřené tepny než muži (kombinovaný endpoint: perioperační mortalita, recidiva iktu a reokluze ošetřené tepny) 14% u žen a 3.9% u mužů (p=0.008) [60].

V klinické praxi jsou zavedeny dvě revaskularizační techniky, karotická endarterktomie (CEA) a perkutánní angioplastika karotid (CAS). V literatuře je dále zmiňován extrakraniální-intrakraniální bypass, tato metoda se v klinické praxi uplatňuje jen marginálně. Karotická endarterktomie je dlouhodobě zavedená invazivní metoda spočívající v chirurgickém odstranění endarteria. Novější a významně se rozvíjející metodou je perkutánní angioplastika karotid. Tato metoda je méně invazivní a byla původně koncipována pro polymorbidní skupiny pacientů, kteří nemohli bezpečně podstoupit chirurgický výkon. Většina studií zaměřených na CAS a srovnání této metody s CEA byla sponzorována komerčními subjekty a

je nutné na jejich výsledky nahlížet kriticky, nicméně s vývojem nových technologií a zvyšující se erudicí intervenčních lékařů se tato metoda stala prakticky rovnocennou k CEA. První větší studií, která srovnávala CEA a CAS, byla CAVATAS (Carotid and Vertebral Artery Transluminal Angioplasty Study) [61]. Tato studie prokázala, že 30 denní mortalita a recidiva iktu u pacientů, kteří postoupili CAS nebo CEA, je srovnatelná (kolem 6%). Limitací této studie bylo použití prosté angioplastiky bez implantace stentu u více než 75% pacientů, kteří podstoupili CAS. Další v literatuře zmiňovanou studií byla SAPPHIRE (Stenting and Angioplasty With Protection in Patients at High Risk for Endarterectomy). Zde již byly použity pokročilejší technologie včetně implantace stentu a aplikace protekce periprocedurální embolizace mozku. Použití CEA vedlo k nižšímu výskytu kombinovaného cíle (mortalita, recidiva iCMP a periprocedurální IM) v prvním měsíci sledování (9,9% pro chirurgickou metodu a 4,4% pro intervenční). Stejný trend na hranici statistické významnosti byl sledován i po 1. roce sledování (20,1% a 12,2%, P=0,05) [62]. V podskupině vysoce rizikových pacientů byly výsledky obou metod srovnatelné a předpoklad vhodnosti CAS u vysoce rizikových pacientů tedy nebyl potvrzen. Mimo jiné výskyt periprocedurálních komplikací zatím stále překračoval hypotetická rizika u asymptomatických pacientů se stenózou obdobného rozsahu léčených konzervativně. Efekt „preventivní“ CAS u asymptomatických pacientů zatím nevyváží periprocedurální rizika výkonu, což je dalším důvodem asymptomatické stenózy k revaskularizaci spíše neindikovat. Ani další rozsáhlé studie neprokázaly statisticky významně lepší efektivitu jedné či druhé metody. Nicméně ze subanalýz jednoznačně vyplývá, že CAS je u pacientů ve vyšším věku provázena nárůstem rizika komplikací a naopak lepší výsledky přinášel CAS u mladších pacientů. Relativní riziko komplikací při CAS ve srovnání s CEA bylo ve věku > 65 let 0,6 ((95% CI, 0.31–1.18), pro pacienty ve věku 65 – 74 let 1.08 (95% CI, 0.65–1.78) a ve věku ≥ 75 let 1.63 (95% CI, 0.99–2.69). Z výše uvedených výsledků vyplývá, že u pacientů ve vyšším věku se jeví jako

výhodnější CEA oproti CAS. Souhrnné doporučení týkající se indikace revaskularizace karotid v sekundární prevenci iCMP a TIA uvádíme v souhrnné tabulce převzaté z aktuálních doporučených postupů [8]:

U pacientů po iCMP či TIA v posledních 6 měsících a s ipsilaterální významnou stenozou karotických tepen (70% - 99%) se doporučuje provedení karotické endarterktomie (CEA) při odhadovaném perioperačním riziku < 6%.	I; *LoE A*
U pacientů po nedávno proběhlé iCMP či TIA a s ipsilaterální středně významnou stenozou karotických tepen (50% - 69%) potvrzenou druhým zobrazovacím vyšetřením se doporučuje provedení karotické endarterktomie v závislosti na individuálních faktorech a při odhadovaném perioperačním riziku < 6%.	I; *LoE B*
Při stenóze < 50% se CEA a karotická angioplastika a stentáž (CAS) nedoporučuje.	III.; *LoE A*
CAS je vhodná jako alternativa k CEA u pacientů s nízkým až průměrným rizikem komplikací spojených s endovaskulární léčbou u významné stenózy a. karotis (>70%) dle zobrazovacích metod při odhadovaném periprocedurálním riziku < 6%.	IIa; *LoE B*
Při revaskularizačním výkonu u pacientů po TIA či iCMP menšího rozsahu je vhodnější při absenci kontraindikací provést výkon do 2 týdnů od příhody než ho odkládat.	IIa; *LoE B*
Při volbě mezi CEA a CAS je vhodné přihlédnout k věku pacienta a anatomii postižené tepny. CEA je u starších pacientů spojena s lepší prognozou než CAS, zvláště při anatomii tepen nevhodných k endovaskulární terapii. U mladších pacientů je CAS rovnocenná k CEA.	IIa; *LoE B*
U pacientů s významnou, symptomatickou stenózou > 70%, se složitými anatomickými poměry, s restenózou po CEA nebo při stenóze po ozáření je vhodné provést CAS.	IIa; *LoE B*
Ve výše uvedených indikacích CEA a CAS musí daný výkon provádět operatér s prokázanými zkušenostmi s periprocedurální CMP a s mortalitou < 6%, podobně jako v ramdomizovaných studiích.	I; *LoE B*
Optimální nechirurgická léčba zahrnuje podávání antiagragancií, statinů a úpravu dalších rizikových faktorů dle příslušných doporučení.	I; *LoE A*

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2.7 Antiagregační léčba

Protidestičková léčba představuje základní farmakologické opatření sekundární prevence všech typů aterovaskulárních chorob. Antiagregační léčba je považována za paušální opatření a vlastní účinek není v naprosté většině případů dále nijak ověřován či monitorován. Nelze tedy hovořit vysloveně o intervenci rizikového faktoru (patofyziologický korelát na úrovni tvorby trombu na povrchu aterosklerotického plátu zde samozřejmě existuje).

Aspirin (ASA) jako stále nejčastěji užívaná látka s antiagregačním účinkem působí především cestou blokády tromboxanového receptoru trombocytu (jakkoliv zasahuje do agregace destiček i v jiných bodech). Jeho indikace v sekudnární prevenci ICHS je prokázána a akceptována již od 80. let minulého století, ale později byl jeho přínos řadou studií potrvzen i u dalších forem aterovaskulární choroby. Jmenovitě pro sekundární prevenci CMP, v meta-analýze těchto studií s 5228 pacienty byla tato léčba spojena s významnou asi 15% redukcí rekurentních příhod [63]. Efekt ASA se z hlediska prevence rekurentních příhod nelišil co do dávky (a ta byla testována ve velmi širokém rozmezí 50-1500 mg), ale z hlediska bezpečnosti by tato dávka neměla přesahovat 325 mg (a pro praxi je asi nejvhodnější zavedené dávkování, jako v případě ICHS, tj. 75-100mg denně).

Druhé nejběžnější antiagregans představuje clopidogrel, jehož mechanismem účinku je blokáda ADP-dependentní agregace destiček, zprostředkovaná receptorem P2Y12 na povrchu trombocytu. Clopidogrel nebyl nikdy testován v sekundární prevenci oproti placebu, ale existují srovnání s monoterapii ASA a dále s duální antiagregační léčbou (DAPT) ASA+ clopidogrel. Ve studii CAPRIE byl srovnáván clopidogrel s ASA u víc než 19 000 pacientů s manifestní aterovaskulární chorobou včetně stavu po CMP a vykazoval jen o něco vyšší, ale již statisticky signifikantní benefit (necelých 9%) ve smyslu redukce velkých kardiovaskulárch příhod (major adverse cardiovascular event, MACE). Na druhé straně, tento rozdíl nebyl speciálně v podskupině pacientů po iCMP signifikantní [64]. Otevřenou otázkou

zůstala ale duální antiagregace clopidogrel *plus* aspirin (tak, jak je to standardem prvních 12 měsíců po akutním infarktu). Studie CHARISMA [65] zahrnovala více než 15 000 pacientů opět s různými formami aterovaskulární choroby, včetně stavu po CMP. Monoterapie clopidogrelem vykazovala tentokrát u pacientů s cerebrovaskulární chorobou v této studii superioritu oproti monoterapii aspirinem. Naopak duální antiagregace se ukázala méně bezpečná než monoterapie clopidogrelem, při prakticky stejné účinnosti. Tato studie doplnila a upřesnila výsledek o něco starší studie MATCH, která srovnávala monoterapii clopidogrelem oproti duální antiagregaci u asi 7600 pacientů po ischemické CMP či TIA a která neprokázala zásadnější benefit kombinační (duální) terapie [66] (a právě na základě těchto výsledků byla posléze upravena Doporučení pro sekundární prevenci cerebrovaskulárních chorob).

Třetím možným modelem antiagregační léčby je duální terapie aspirin + dipyridamol. Dipyridamol zasahuje do agregace destiček na několika úrovních, včetně ovlivnění inhibitoru fosfodiesteráz 5 a prostacyklinu . Přinejmenším 4 velké randomizované studie porovnávaly (kromě jiného) efekt monoterapie ASA a duální terapie ASA+ dipyridamol u pacientů po cerebrovaskulární příhodě. Souhrnně lze konstatovat, že kombinační léčba vykazuje v sekundární prevenci lepší ochranu z hlediska incidence MACE než monoterapie [67-69]. Na druhou stranu, dipyridamol je obecně pacienty poměrně špatně tolerován, což odráží i jeho zcela mizivá preskribce v klinické praxi. V tomto směru je také zajímavý výsledek studie ProFESS, která srovnávala monoterapii s clopidogrelem oproti duální léčbě dipyridamol+ASA. Monoterapie se ukázala stejně účinná s hlediska zabránění rekurentní CMP a navíc kombinační léčba byla spojena s vyšší (byť ne signifikantní) incidencí hemorhagických příhod. [70] Lze tedy konstatovat, že monoterapie clopidogrelem se v čistém klinickém přínosu (net clinical benefit) zatím jeví obecně jako nejvýhodnější.

Základní principy ze současně platných Doporučení [8] shrnuje opět tabulka:

Všichni pacienti po nekardioembolické CMP by měli užívat antiagregační léčbu spíše než antikoagulační.	I; *LoE A*
Přijatelné varianty jsou buď monoterapie s aspirinem, kombinační léčba aspirin+dipyridamol nebo monoterapie clopidogrelem.	I; *LoE A* I; *LoE B* IIa; *LoE B*
Není žádný důkaz, že by zvyšování dávky aspirinu mělo nějaký přínos, stejně tak efekt nepřináší ani přidání antiagregační léčby k antikoagulační. Tato terapie je přijatelné pouze ve speciálních situacích (zejména po aplikaci koronárního stentu).	IIb; *LoE C*
Duální léčba aspirin+clopidogrel je přijatelná do 90 dnů po drobné CMP, ale pro dlouhodobé podávání je spojená s nárůstem hemorhagických iktů a není dopoučována .	IIb; *LoE B* III; *LoE A*

2.8 Další faktory

Existuje jistě celá řada dalších faktorů zasahujících do etiologie cerebrovaskulárních chorob (a význam některých z nich může být zcela kruciální), které nejsou v tomto souhrnu uvedeny. Bezesporu nejzásadnější z nich, ale bohužel kompletně neovlivnitelný, je věk pacientů (správnější by ale bylo říci „biologický věk“) – cerebrovaskulární choroby jsou zejména chorobou vyššího věku a je celkem jasné, že i jenom kvůli tomu je prognóza pacientů po CMP méně příznivá, než je tomu u ostatních forem aterovaskulárních chorob. Nelze popřít ani význam dalších konvenčních rizikových faktorů aterosklerozy- především obezity a fyzické neaktivity. V tomto případě ale platí stejná obecná režimová doporučení, jako je tomu např. v případě ICHS - a o jejich reálné implementaci do klinické praxe si není dobré činit iluze (což však nesnižuje jejich evidentní účinnost).

Dále je zde celá řada dalších chorob s prokazatelně zvýšeným rizikem CMP. Zařadit je sem možno např. obstrukční spánkovou apnoe, aneurysma aorty, valvulární chorobu srdeční a některé kardiomyopatie, foramen ovale patens, ale i choroby spojené hyperkoagulačním stavem a také některé jinak zdánlivě nesouvisející choroby (např. chronická renální insuficience). Celkový dopad těchto faktorů na péči v sekundární prevenci je spíše limitovaný, nejsou zde již jednotlivě rozebírány.

SOUHRN SOUČASNÝCH MOŽNOSTÍ LÉČBY ISCHEMICKÉ CÉVNÍ MOZKOVÉ PŘÍHODY V AKUTNÍM STÁDIU

3.1 Akutní management

Akutní management u pacientů s ischemickou CMP a TIA je z hlediska záchrany motorických i kognitivních funkcí naprosto zásadní. Neurony jsou extrémně citlivé na hypoxii a při typickém uzávěru mozkové tepny dochází každou minutu ke ztrátě 1.9 milionu neuronů [71]. Rozsah ischemie a rychlost rozvoje nekrózy je reálně dána více faktory, mezi které patří kolaterální řečiště, reziduální průtok a kalibr postižené arterie, reologické vlastnosti krve, aktivace koagulačního a fibrinolytického systému. Tímto mechanismem dochází k rozvoji oblasti centrálního nervového systému (zóna penumbry), která je v dané chvíli afunkční, nicméně při reperfuzi je schopna své funkce postupně opět obnovit. Naopak při pozdní reperfuzi již nekroticky změněné tkáně nedojde k restituci funkce, ale k dalšímu strukturálnímu poškození s vysokým rizikem hemorhagické transformace iktu. Z výše uvedených důvodů je v doporučených postupech zcela pochopitelně na prvním místě zdůrazňována rychlost a organizace péče s co nejkratší dobou do zahájení reperfuze [72]. Jedním z nejslabších míst je vlastní období před aktivací záchranného systému. Méně než polovina pacientů postižených akutním iktem aktivuje záchranný systém s odstupem delším než 1 hodinu od začátku symptomů a u více než poloviny pacientů k tomu vedla neznalost příznaků mozkové příhody. Zde doporučení apelují na maximální intenzitu edukace širší populace, která by mohla vést ke zlepšení léčebných výsledků. V posledním desetiletí vlivem centralizace a organizace akutní péče došlo k zásadnímu rozšíření počtu pacientů, u kterých bylo možno provést reperfuzní terapii [72,73]. Doporučenými postupy České neurologické společnosti a standardy ministerstva zdravotnictví je přesně definován postup záchranného systému, síť center delegovaných k podání fibrinolytické terapie a též síť komplexních

cerebrovaskulárních center, která by měla disponovat též intervenčními metodami s dostupností 24 hodin denně a neurochirurgickým zázemím.

3.2 Reperfuzní léčba

Základními metodami reperfúzní léčby akutního ischemického iktu jsou systémová fibrinolýza a nově také lokální trombolýza a mechanická trombektomie. Fibrinolytika působí jako aktivátory plasminogenu, aktivují endogenní fibrinolytický systém. Aktivace plasminogenu na plasmin vede k následnému štěpení fibrinu, ale i fibrinogenu a f. V a VIII. koagulační kaskády. Fibrinolytická terapie (nebo také systémová trombolýza) byla americkým úřadem pro kontrolu léčiv schválená k léčbě iCMP již v roce 1996 na základě výsledků studie NINDS rtPA Stroke Trial [74]. Tato studie (resp. její druhá část „PART II.“) ukázala, že podání systémové fibrinolýzy do 3 hodin od rozvoje neurologických příznaků vede k významně vyšší plné či částečné restituci motorických funkcí v odstupu tří měsíců od primární příhody (OR, 1.9; 95% CI, 1.2–2.9), ale též po 1 a 3 letech sledování. Stinnou stránkou podání trombolýzy však byl signifikantní nárůst intracerebrální hemorhagie ve srovnání s placebem (6,4% versus 0,6%), který ale nevedl ke zvýšení mortality po třech měsících ani po 1 roce sledování [74]. V dalším časovém sledu proběhlo množství randomizovaných studií, které vedly ke zpřesnění výběru adeptů léčby a ustálení terapeutického okna podání systémové trombolýzy kromě výjimečných situací na dobu 4,5 hodin (podrobnější informace o trombolytické terapii přesahují rámec této práce). Jakkoliv je trombolytická léčba účinným nástrojem léčby, musí být při rizikovosti v podobě fatálních krvácivých komplikací vedena uvážlivě a pouze vysoce erudovaným profesionálem.

Novým terapeutickým nástrojem akutní léčby iCMP je mechanická trombektomie. Rozvoj intervenčních metod léčby iCMP přímo navazoval na potřeby minimalizace krvácivých

komplikací fibrinolytické léčby, což vedlo k zavádění transkatetrové lokální trombolýzy přímo do trombotického uzávěru. Bezpečné terapeutické okno u této formy léčby se ukázalo být delší než při systémovém podání a současná guidelines umožňují použití do 6 hodin od vzniku symptomů. Testování technických systémů k provádění vlastní mechanické trombektomie intenzivněji probíhalo od roku 2007. První úspěšná klinická studie byla publikována v roce 2014 [75] a další studie její výsledek potvrdily. Jak ukázala jejich meta-analýza z roku 2015, ve srovnání s trombolýzou trombektomie zvyšuje šanci na dobrý výsledný funkční stav (modifikované Rankinovo skore 0–2) asi o 71% ($p = 0,005$), zatímco šance na úspěšnou revaskularizaci je až 6x vyšší ($p < 0,001$) [76]. Principem této metody je mechanické odstranění trombu (embolu) z velké mozkové tepny (typicky arteria cerebri medea) pomocí intraarteriálně zavedeného katetru. Limitací této metody je užší spektrum vhodných pacientů, vznik sekundárních embolizací při odstraňování trombu, vysoká náročnost na technické vybavení a personální obsazení pracovišť. Podle dostupných analýz se mechanickou trombektomii dařilo realizovat u 12 % až 48,5 % pacientů z celkového počtu ischemických mozkových příhod [77,78]. I díky enormnímu zájmu komerčních subjektů dochází k intenzivnímu rozvoji stále sofistikovanějších léčebných systémů a již implementované postupy kombinující fibrinolytické a intervenční metody léčby jsou příslibem dalšího pozitivního posunu v péči o pacienty s ischemickou cévní mozkovou příhodou. Na druhé straně je zcela evidentní, že i nejmodernější přístup v akutní péči má své nepřekonatelné limity, dané především časovým faktorem.

3.3 Podpůrná terapie

Mimo specifickou terapii akutního iktu hraje svoji roli v akutní péči o pacienty s iCMP a TIA také léčba podpůrná. Zde je nutné samozřejmě zmínit problematiku arteriální hypertenze. Optimální hodnoty krevního tlaku v akutní fázi ischemického iktu nebyly

dosud zjištěny. Extrémně vysoké hodnoty krevního tlaku významně zvyšují riziko rozvoje hypertenzní encefalopatie, hemorhagické transformace iktu, srdečního a renálního selhání. Lehce zvýšené hodnoty krevního tlaku pravděpodobně zvyšují perfuzi v ischemizovaných oblastech centrální nervové soustavy. Naopak extrémní hypotenze vede ke generalizované hypoperfuzi, která se projeví zejména v ischemizovaných částech nervového systému. Souhrnně studie zatím prokázaly, že rozmezí krevního tlaku, které predikuje nejpříznivější klinický outcome pacientů, se nalézá mezi 121 – 200 mmHg systolického krevního tlaku a 81 – 110 mmHg tlaku diastolického (což je natolik široké rozmezí, že bude vyžadovat ještě další zpřesnění). V různých studiích byly také testovány odlišné protokoly léčby či preferována jednotlivá antihypertenziva (například blokátor kalciového kanálu). Nic z toho však k významnějšímu průlomu v léčbě nevedlo a v prvních 24 hodinách se doporučuje aktivní snižování krevního tlaku pouze při hodnotách >220/120 mmHg. [8] Pouze v případě aplikace systémové trombolýzy jsou postupy terapie udávány přesněji. V případě indikace podání systémové trombolýzy je doporučeno udržovat hodnoty krevního tlaku <180/105 mmHg dle specifických protokolů. Obnovení antihypertenzní terapie u hypertoniků léčených již před mozkovou příhodou je možné po uplynutí 24 hodin za podmínky plné neurologické stability. Z dalších podpůrných terapeutických postupů je doporučována korekce hypovolémie a hypotenze, udržování euglykémie a normotermie [8]. Diskutabilní je i paušální podávání kyslíku. Značná část studií, zejména u pacientů s normoxémií, totiž neprokazuje žádný benefit z aditivního podávání kyslíku [79,80].

II. SOUHRN VLASTNÍCH VÝSLEDKŮ

1. VÝCHODISKO ŘEŠENÉ PROBLEMATIKY

Deklarovaným konečným cílem péče o pacienty s již manifestovanými kardiovaskulárními (KV) chorobami aterosklerotické etiologie (tj. tzv. sekundární prevence) je redukovat riziko fatality a incidence rekurentních KV příhod, prodloužit tak individuální dobu života osob postižených těmito chorobami, a to ideálně při zachované plné fyzické i duševní funkční kapacitě. Neméně důležitými cíli jsou však i pokles dlouhodobých komplikací (v případě koronární manifestace např. srdečního selhávání), manifestací aterovaskulární choroby v jiných lokalizacích, potřeby revaskularizací a v neposlední řadě celkové zlepšení kvality života pacientů. Základní principy, jak dosáhnout tohoto cíle, jsou extenzivně definovány sérií pravidelně obnovovaných tzv. Společných evropských doporučení („Guidelines“) pro prevenci kardiovaskulárních chorob již od roku 1994. [2-7] Počínaje třetí revizí jsou tato Doporučení [4] považována za jednu ze základních priorit i efektivní opatření u pacientů s cerebrovaskulárními chorobami (tj. zejména po ischemické cévní mozkové příhodě). Konkrétní realizace těchto opatření spočívá na prakticky stejných principech jako sekundární prevence ischemické choroby srdeční (ICHS), tj. léčebné ovlivnění základních rizikových faktorů k definovaným cílovým hodnotám a dále pak paušální preskribce vybrané farmakoterapie.

Nakolik jsou principy sekundární prevence do klinické praxe implementovány, popisuje poměrně unikátně už řadu let projekt EUROASPIRE (European Action on Secondary Prevention by Intervention to Reduce Events). Ten byl zahájen v roce 1995/96 a další identické přůřezové studie (deskriptivní surveye) následovaly v letech 1999/2000, 2006/7 a 2012/13 (tj. EUROASPIRE II-IV [81-84] [7-9] (a aktuálně probíhá již i studie EUROASPIRE V). Výsledky těchto studií demonstrovaly vysokou prevalenci neadekvátně kontrolovaných modikovatelných rizikových faktorů a insuficientní preskribci základní farmakoterapie v sekundární prevenci ICHS (a to v celé Evropě, včetně České republiky). Srovnatelná data pro

ceberovaskulární choroby prakticky neexistovala, dokud tzv. “stroke specific modul” nebyl realizován jako substudie EUROASPIRE III. Z výsledků této substudie [85] vyplynulo, že principy sekundární prevence jsou do klinické praxe u pacientů po první ischemické CMP implementovány ještě daleko hůře, než je tomu v případě sekundární prevence ICHS. Druhá podobná deskriptivní studie u pacientů po ischemické CMP (ESH Stroke survey) byla realizována v letech 2012-13 podle prakticky identického protokolu [11] a v České republice navíc ve stejných centrech, což nám umožňuje posoudit vývoj v čase. Právě česká data z posledních dvou jmenovaných projektů (tj. EUROASPIRE III- stroke a ESH Stroke survey) jsou hlavním zdrojem předkládaných výsledků této disertační práce.

2. CÍLE ANALÝZY A ZÁKLADNÍ ŘEŠENÍ OTÁZKY

Základním cílem naší analýzy bylo stanovit, nakolik jsou do reálné klinické praxe implementovány principy sekundární prevence u pacientů po první ischemické cévní mozkové příhodě z hlediska kontroly konvenčních rizikových faktorů, zdali je zde v průběhu času pozorovatelná nějaká změna a nakolik mohou riziko u pacientů ovlivnit další okolnosti (nekonvenční rizikové faktory). Položili jsme si tedy následující konkrétní otázky:

- nakolik je reálně kontrola konvenčních rizikových faktorů v souladu s cílovými hodnotami, definovanými platnými Doporučeními, a to ve vzorku stabilizovaných pacientů po první ischemické CMP (český soubor mezinárodní multicentrické studie ESH-stroke survey z roku 2012)

- nakolik se kontrola konvenčních rizikových faktorů změnila v průběhu mezi lety 2007 a 2013 (tj. v průběhu doby, kdy by mělo teoreticky dojít k již plné implementaci principů formulovaných dle Doporučení) a zdali je zde pozorovatelný alespoň trend k zlepšení v celkové mortalitě.

- nakolik se liší kontrola konvenčních rizikových faktorů u stabilizovaných pacientů po ischemické CMP a s ICHS (tj. po infarktu myokardu a/nebo koronární revaskularizaci, včetně korespondujícího mortalitního rizika)

- nakolik mohou stav či osud pacientů ovlivnit další (nekonvenční) faktory

3. METODA

3.1 Design studie a studovaná populace

Jednotlivé dílčí analýzy jsou koncipovány jednak jako deskriptivní průřezová (cross-sectional) studie, jednak prospektivní mortalitní studie. Studie byla realizována vesměs na plně stabilizovaných pacientech, tj. minimálně 6 měsíců po zařazovací akutní vaskulární příhodě (1. ischemické CMP, resp. infarktu myokardu a/nebo koronární revaskularizaci pro jednu s dílčích analýz). Použity byly dobře definované české soubory mezinárodních multicentrických průzkumů (surveyí), tj. ESH-stroke survey z let 20012-13, EUROASPIRE-stroke module z roku 2007, a dále EUROASPIRE III a IV ze stejných časových období. Výběr vzorků respektoval centrální protokoly výše zmíněných surveyí, ale fakticky vycházel z identických principů (takže všechny vzorky jsou vzájemně srovnatelné), detailněji je to popsáno jinde. [11,85]

Pacienti s diagnózou ischemické CMP mladší 81 let byli identifikováni na základě propouštěcích zpráv, přičemž definice respektovala kritéria Světové zdravotnické organizace WHO [86] a ischemická etiologie musela být iniciálně (tj. v úvodu/během hospitalizace) verifikována zobrazovací metodou (výpočetní tomografií či magnetickou rezonancí mozku). Do analýzy nebyli dále zařazeni pacienti s rekurentními CMP (i když předcházející transitorní ischemická ataka byla akceptovatelná), sekundární hemorhagickou transformací, dále pak pacienti žijící dlouhodobě mimo sledovaný region a ti co zemřeli již během úvodní hospitalizace. Identifikace jednotlivých probandů byla realizována retro-konsekutivně (tj. zahájena byla s nejrecentnějšími případy a postupováno bylo zpětně v čase), dokud nebylo dosaženo plánovaného souboru ~ 500 pacientů.

Soubor s ICHS (použitý pro jednu ze subanalýz) zahrnoval pacienty hospitalizované pro některou z následujících situací: akutní nebo elektivní koronární bypass či perkutánní

koronární angioplastika, akutní infarkt myokardu nebo prokázaná koronární ischemie (dle závěru ošetřujícího lékaře). Výběr pacientů (resp. verifikace zařazovací diagnózy) byl proveden na základě informací v propouštěcí zprávě pacienta a zařazeni byly pouze ti pacienti, kteří byli v době vyšetření mladší 81 let. Identifikace pacientů byla zahájena u nejrecentnějších případů, ale ne dříve než 6 měsíců po příslušné hospitalizaci, a pokračovala zpětně v čase, dokud nebylo (v každé z primárních studií) dosaženo počtu 600 pacientů.

Pro jednu z realizovaných analýz byla také použita srovnávací skupina z obecné populace. Tu představoval soubor věkově vyvážených subjektů, vyšetřených v rámci populační studie postMONICA [11] (bližší detaily viz příslušná publikace v příloze).

Všechny studie byly realizovány ve dvou stejných centrech, tj. ve Fakultní nemocnici Plzeň a Institutu klinické a experimentální medicíny, která představují zdravotnická zařízení univerzitního typu poskytující všechny typy kardiologické péče (tj. péče o akutní stavy ICHS, intervenční kardiologii a kardiochirurgii) se spádovou oblastí více než 500 000 obyvatel.

3.2 Vyšetřovací procedury

Všechny vyšetřovací procedury byly realizovány podle standardních protokolů příslušných studií [ESH stroke survey a EUROASPIRE]. Vyšetření obsahovalo základní demografické charakteristiky, individuální rodinnou a osobní anamnézu kardiovaskulárních chorob, detailní informace o životním stylu a užívané farmakoterapii. Dále proběhly následující vyšetřovací procedury: měření tělesné výšky a hmotnosti v lehkém spodním prádle pomocí automatických vah SECA 701 (SECA GmbH, Hamburg, Německo) s připojeným měřidlem (váhy byly náležitě kalibrovány vždy před zahájením každé ze studií). Obvod pasu byl měřen ocelovou krejčovskou mírou v místě největšího objemu trupu.

Krevní tlak (TK) byl měřen standardním rtuťovým sphygmomanometrem (ERKA-tech, Bad Tölz, Německo) vsedě po 5 minutách v klidu s nasazenou manžetou. Použit byl průměr ze

dvou měření provedených s odstupem alespoň 2 minut, přičemž pokud rozdíl obou měření přesahoval 10 mmHg, byla provedena ještě další měření (a pro výpočet průměru použity poslední 2 hodnoty). U pacientů s obvodem paže vyšším než 35 cm byla použita široká manžeta.

Kuřácký habitus byl ověřován pomocí přístroje SMOKERLYSER (Bedfont Scientific, Upchurch, Velká Británie) na základě počtu vydechovaných částic oxidu uhelnatého (ppm).

Orientační neurologický deficit v době vyšetření (tj. evidentní afázie, dysfázie, pareza/plegie končetin či v obličeji nebo udávaný senzitivní deficit) byl posuzován vyšetřujícím lékařem (internistou), zatímco individuální funkční kapacita objektivizována jako Barthelův ADL (activities of daily living) Index. [87] Standardní 12-svodové EKG bylo registrováno se zaměřením zejména na přítomnost fibrilace či flutteru síní.

Odběr krve byl realizován z venepunkce po přinejmenším 12-ti hodinovém lačnění. Laboratorní vyšetření bylo realizováno vesměs v sériích z alikvotů zamražených při teplotě -80^0 C. U všech proband byly v seru stanoveny přinejmenším následující analyty: celkový (TCHOL) a HDL cholesterol (HDL), triglyceridy (TG), glukoza a B typ natriuretického peptidu (BNP), a to pomocí komerčních kitů a analyzátoru ARCHITECT c800 (Abbott Laboratories, Wiesbaden, Německo). LDL cholesterol byl kalkulován pomocí Friedewaldovy rovnice, tj. LDL= TCHOL-HDL-(TG/2.22). Detaily dalších jednotlivých sub-analýz jsou uvedeny v příslušných publikacích v příloze.

Všichni pacienti byli v rámci realizovaného klinického vyšetření vyzváni také k vyplnění jednotného „Anamnestického dotazníku," zaměřeného na psychický a somatický stav, včetně některých specifických projevů kardiovaskulární choroby. Dotazník pacienti vyplňovali v největší míře sami v období před klinickým vyšetřením (v rámci čekání), pouze v případě nejasností, chybění některých odpovědí či fyzické inkapacity pacienta (špatný zrak, paréza

končetiny..) byl dotazník dokompletován za pomoci některého z vyšetřujících zdravotníků (obvykle vyšetřujícího lékaře). Ke stanovení depresivního či anxiozního ladění byl použit standardizovaný dotazník Hospital Anxiety Depression Scale (HADS)[88]. Kvalita života byla kvantifikována pomocí dotazníku SF-36 (Short Form-36) [89]. Anginozní potíže byly zjišťovány a objektivizovány na základě modifikovaného Roseova dotazníku [90].

3.3 Zpracování dat

Body mass index (BMI) byl kalkulován jako poměr tělesné hmotnosti v kilogramech a čtverce tělesné výšky v metrech. Aktivní kouření bylo definováno buď jako pozitivní anamnestický údaj či více než 10 ppm oxidu uhelnatého ve vydechovaném vzduchu (na základě měření přístrojem Smokerlyser).

Pro kategorizaci konvenčních kardiovaskulárních rizkových faktorů bylo použito jejich cílových hodnot tak, jak byly stanoveny recentními Společnými evropskými doporučeními pro prevenci kardiovaskulárních chorob [7], tj.: nadváha, BMI ≥25 kg/m^2 či obezita BMI ≥30 kg/m^2; zvětšený obvod pasu jako ≥ 102 cm u mužů či ≥ 88 cm u žen; zvýšený krevní tlak (TK) jako systolický TK ≥140 mmHg a/nebo diastolický TK ≥ 90 mmHg; hypercholesterolemie jako LDL ≥ 1.8 mmol/L, nízké HDL jako < 1.0 mmol/L u mužů nebo <1.2 mmol/L u žen; hypertriglyceridemie jako TG ≥ 1.7 mmol/L neadekvátní kontrola glykemie jako lačná glykemie ≥ 7 mmol/L a/nebo HbA1c ≥ 48 mmol/mol. Pokud došlo v průběhu času ke změně cílové hodnoty (jako např. v případě LDL), použity byly obě hodnoty. Zvýšené BNP jsme arbitrárně stanovili jako ≥ 100 ng/mL. Jako „angina pectoris“ byly vyhodnoceny korespondující potíže, pokud se vyskytovaly alespoň 1x týdně. Za “reziduální motorický deficit” byl považován pouze nález parézy či plegie končetiny. HADS skore pro depresi a anxiozitu bylo kategorizováno v souladu se zavedeným standardem do 3 podskupin (pro každou z obou dimenzí zvlášť): normální habitus při skore 0-7, hraniční (mírné) depresivní ladění při skore 8-10 a jistá deprese či anxiozita při skore 11 a výše. Hodnoty SF skore byly užity převážně v kontinuální

podobě, ale pro potřeby výpočtu relativního rizika jednotlivých prediktorů kvality života byla použita arbitrární hranice celkového SF skore ($SFscore_{total)}$ <40 (tj. ≈nejnižší kvartil distribuce tohoto parametru).

Pro potřeby prospektivních analýz byla zjištěna mortalita v souboru k určitému fixnímu datu, a to na základě registru Ústavu zdravotnických informací a statistiky. ICD-10 klasifikace v úmrtních listech byla použita ke specikaci deklarované základní příčiny úmrtí. Kalkulace statistické síly velikosti vzorku stanovila, že náš vzorek byly suficientní k posouzení 5-tileté mortality s 5% relativní přesností.

Statisticky byla data testována pomocí software STATISTICA 8 a STATA/SE 8, přičemž použity byly standardní postupy deskriptivní metody, metodiky nepárového porovnání nezávislých vzorků (Mann-Whitney U test a χ^2 test) a dále pak standardní regresní modely (mnohočetná lineární či logistická regrese a Coxův regresní model proporcionálních rizik pro potřeby mortalitních analýz). Bližší detaily statického zpracování jsou opět uvedeny v příslušných publikacích.

3.4 Etické aspekty

Všichni pacienti zahrnutí do analýzy podstoupili vyšetřovací program na základě dobrovolnosti a jedině v případě podepsání Informovaného souhlasu. Všechny zahrnuté projekty byly projednány a schváleny lokální Etickou komisí. Všechna data jsou skladována v souladu se Zákonem na ochranu osobních dat a všechny procedury byly realizovány podle zásad Správné klinické praxe.

4. SOUHRN VLASTNÍCH VÝSLEDKŮ

Následující sekce uvádí výsledky jednotlivých subanalýz (podle položených vědeckých otázek) v sumarizované podobě – blíže jsou výsledky rozebrány a diskutovány opět v přiložených publikacích.

4.1. Kontrola konvenčního rizikového profilu pacientů po ischemické CMP

V této sub-analýze bylo hodnoceno celkem 424 pacientů o průměrném věku 66.0 (±SD 10.4) let, 60.6 % tvořili muži (repondence činila 73.9%). Jednalo se o pacienty minimálně 6 měsíců po 1. atace ischemické CMP (nejvíce z nich bylo kardioembolické etiologie). Tato kapitola představuje v podstatě jen základní deskriptivní analýzu českého souboru projektu ESH stroke survey z let 2012-13.

Z hlediska úvodního managementu (tj. v době hospitalizace pro zařazující příhodu) 41.8% pacientů bylo iniciálně hospitalizováno na specializované iktové jednotce (primárně ti z Plzeňského centra projektu), 22.2% obdrželo iniciálně intravenozní trombolýzu a 1.9% podstoupilo mechanickou rekanalizaci.

Celkem 23.8% pacientů aktivně kouřilo (63.6% z těch co byli kuřáky v době manifestace CMP), 42% bylo obezních, resp. 82.1% mělo zvětšený obvod pasu. Ačkoliv alespoň jedno antihypertezívum užívalo více než 88% pacientů, náležitě kontrolovaný krevní tlak (méně než 140-90) mělo jen 33.4% ; na druhé straně prevalence těžké hypertenze (≥180/110) ale zase jen 13.2%. Na kontrolu hypercholesterolemie lze pohlížet dvěma způsoby- pokud použijeme v době vyšetření již platnou, ale nikoliv asi ještě plně implementovanou přísnější cílovou hodnotu LDL méně než 1.8 mmol/L. Této hodnoty dosáhlo jen asi 14% pacientů. Starší a benevolentnější cílové hodnoty méně než 2.5 mmol/L dosahovalo asi 42% pacientů. Kromě toho asi 30% subjektů vykazovalo hypetriglyridemii a asi 50% nízký HDL. Poměrně závažná je situace z hlediska poruchy glukozového metabolismu. Více než 37% pacientů již bylo

možno kategorizovat jako manifestní diabetiky (tj. s glykemií nalačno ≥ 7 mmol/l nebo léčbou antidiabetiky), plus dalších 16.3% plnilo kritéria porušené glykemie nalačno (6.1–6.9 mmol/L). Náležité kontroly glukozového metabolismu (tj. glykemie nalačno ≥7 mmol/l a/nebo HbA1c ≥ 48 mmol/mol) v celém souboru nedosahovalo 37.7% probandů. Permanentní fibrilace (či flutter) síní byla v době vyšetření zachycena u 11.4% subjektů (prevalence paroxysmální fibrilace validně zjistitelná nebyla).

Z hlediska medikace paušálně předepisované v sekundární prevenci vaskulárních chorob bylo 92% pacientů léčeno antiagregační nebo antikoagulační léčbou, na druhé straně jen 18.4% bylo na monoterapii clopidogrelem. Inhibitory angiotensin konvertujícího enzymu (ACEi) či blokátory receptoru pro angiotenzin II (ARB) užívalo necelých 71%, zatímco statiny 62% pacientů. Warfarinizováno bylo 15.4 % pacientů.

V době vyšetření (tj. po plné stabilizaci alespoň 6 měsíců po manifestaci vaskulární příhody) vykazovalo 55% pacientů alespoň minimální neurologický deficit, zatímco 39.4% motorický deficit (tj. paréza či plegie některé z končetin). Prevalence depresivního ladění činila 24%, zatímco anxizita se vyskytovala u přibližně 17% pacientů. Sníženou kvalitu života, definovanou arbitrárně na úrovni celkového SF skore ≤40, vykazovalo v našem souboru 16% pacientů

Další údaje a analýzy jsou v publikacích v příloze 1 a 3.

4.2. Změny úrovně sekundární prevence po ischemické CMP mezi lety 2007 a 2013

Celkem 341 a 424 pacientů po verifikované první ischemické CMP o průměrném věku 69.0 (±SD 9.1) a 66.8 (±SD 10.4) let bylo vyšetřeno v rámci první (2007) a druhé studie (2012-13) a je porovnáváno v předložené analýze. Pokud vyloučíme pacienty, kteří zemřeli mezi propuštěním z hospitalizace a vyšetřením, celková respondence činila v obou studiích 79.3%, resp. 73.9%.

Pokud posuzujeme vývoj adherence k doporučeným cílovým hodnotám jednotlivých rizikových faktorů, signifikantně se mezi lety 2007 a 2012/13 zlepšila pouze kontrola hypercholesterolemie, a to ještě jenom pokud použijeme starší a benevolentnější cílovou hodnotru LDL (tj. méně než 2.5 mmol/L). Naopak významně stoupl (poněkud překvapivě) počet kuřáků a také proporce zvýšeného obvodu pasu. Ostatní základní rizikové faktory se staticky významně nezměnily, a to bohužel včetně kontroly hypertenze, kterou lze v kontextu sekundární prevence považovat za klíčovou. Významně se neměnila (nelepšila) ani kontrola poruchy glukózového metabolismu či její prevalence (tj. 50-60%, což lze považovat za alarmující).

Přece jenom příznivější výsledky dávají data ohledně kurativy. Zásadně stoupla proporce iniciální hospitalizace na iktové jednotce (z cca 7 na 42%) a trombolýz (z cca 2 na asi 22%). V sekundární prevenci skokově narostla preskribce clopidogrelu (v roce 2007 ještě vůbec nepředepisovaného) a mírněji, byť již statisticky významně, i statinů.

Součástí téže studie byla i mortalitní analýza dat z roku 2007. V průběhu 1959 dní (5.4 let) follow-up zemřelo v souboru celkem 97 pacientů (28.5%), z čehož 75 fatálních případů bylo posouzeno jako kardiovaskulární. Korespondující pětiletá celková mortalita činila 25.8%, z toho kardiovaskulární 19.9%. Za pomocí Coxova modelu jsme dále analyzovali relativní váhu jednotlivých (kategorizovaných) konvenčních rizikových faktorů na individuální mortalitní riziko. Zjistili jsme, že po komplexní adjustaci pouze věk přesahující 64 let a suboptimální kontrola glykemie (definovaná jako glykemie nalačno $\geq$ 7 mmol/L a/nebo HbA1c $\geq$ 48 mmol/mol) vstoupily do regresního modelu jako signifikantní prediktory celkové i kardiovaskulární mortality.

Další údaje lze dohledat v publikaci v příloze 1.

4.3. Srovnání úrovně sekundární prevence u pacientů po ischemické CMP a s chronickou ischemickou chorobou srdeční

Tato analýza zahrnovala cekem 1729 pacientů, 765 po první ischmeické CMP (výše analyzované soubory) a 964 se stabilizovanou ICHS (tj. minimálně 6 měsíců po infarktu či koronární revaskularizaci), spojené české soubory EUROASPIRE III a IV) o průměrném věku 67.8 (±SD 9.9) a 64.3 (±SD 9.0) let, resp. Pacienti po CMP byli signifikantně starší a byli častěji ženského pohlaví a častěji kouřili. Méně často byli sledovaní specialistou (neurologem, kardiologem…) a zásadní rozdíl byl i v anamneze revaskularizací (zatímco 94.2% pacientů s ICHS bylo po koronární revaskularizaci, endarterektomie a. carotis byla provedena pouze u asi 5% pacientů po CMP).

Z hlediska adherence k základním principům sekundární prevence pacienti po CMP častěji kouřili, měli vyšší prevalenci zvýšeného obvodu pasu, špatně kontrolované hypertenze a hypercholestrolemie. Naopak neadekvátní kontrola glukozového metabolismu byla zase častější u pacientů s ICHS. Tyto rozdíly přetrvávaly signifikantní i po komplexní adjustaci v mnohočetné logistické regresi.

Pacienti po CMP byli také signifikantně méně často léčeni základní farmakoterapií v sekundární prevenci, tj. antiagregancií, ACEi či ARB a statiny. Přestože fibrilace síní se u pacientů po CMP vyskytovala celkem očekávatelně častěji než u těch s ICHS, antikoagulační léčba byla paradoxně užívaná významně méně (62.5 % versus 94.2%).

Mortalitní analýza byla realizována u 815 subjektů (tj. u těch vyšetřených v letech 2006/07). V průběhu sledování (2050 dní v mediánu) celkem 168 pacientů zemřelo (20.6%), z čehož 126 fatálních příhod (15.5%) bylo posouzeno na základě dostupné dokumentace jako kardiovaskulární etiologie. Korespondující 5-tiletá celková mortalita činila 25.8% u pacientů po CMP, zatímco 13.3% u ICHS, resp. (p=0.0023; χ^2 test), zatímco 5-tiletá kardiovaskulární

mortalita 19.9% *versus* 9.7%, resp. (p=0.013). Signifikantní rozdíly v mortalitě ale bylo možno mezi oběma skupinami pozorovat již po prvním roce od vyšetření [celková mortalita: 4.1% *versus* 1.6%, p=0.031; kardiovaskulární mortalita: 3.8% *versus* 1.0%, p=0.0069)].

Při použití Coxova modelu proporcionálního rizika a po komplexní adjustaci na další rizikové faktory vykazovali pacienti po CMP asi o 85% vyšší riziko celkové mortality či o 89% vyšší riziko kardiovaskulární mortality a to se nezměnilo ani pokud byla v druhém kroku do modelu přidána i užívaná farmakoterapie ACEi/ARB a statiny [plně adjustované HRR pro CMP jako kvalifikující diagnozu činilo 1.78 (95% CI: 1.24-2.55) či 1.83 (95% CI: 1.19-2.77) pro celkovou či kardiovaskulární mortalitu, resp.]

Blíže viz publikace v příloze 2.

4.4 Další dílčí realizované sub-analýzy

4.4.1 Kontrola hypertenze u pacientů po CMP ve srovnání s obecnou populací.

V této sub-analýze byla srovnávána kontrola hyperenze v souboru ESH stroke survey z roku 2012 s věkově/genderově vyváženým souborem obecné populace ze studie post-MONICA (příloha 3). Jak se dalo očekávat, prevalence hypertenze byla u pacinetů po CMP zásadně vyšší než v kontrolní, relativně zdravé populaci (91.5% versus 71.7%). Z hlediska náležité kontroly hypertenze (tj. pod 140/90 mmHg) však obě skupiny vycházely v podstatě podobně špatně (tj. jen 43%, resp. 44% bylo léčeno náležitým způsobem). Z ostatních rizikových faktorů nutno zmínit například takřka dvojnásobnou prevalenci kouření u pacientů po CMP (!).

4.4.2 Trendy celkové mortality po ischemické CMP

Tato analýza byla realizována u celkem 4020 pacientů, hospitalizovaných mezi lety 2003 a 2010 ve Fakultní nemocnici Plzeň s CT verifikovanou ischemickou cévní mozkovou příhodu

(příloha x). Z tohoto velkého souboru celkem 1848 pacientů zemřelo ke 31.12.2011, kdy byl ověřen jejich vitální status. In-hospitalizační mortalita (case-fatality) činila 7%, zatímco 30-ti denní a 1-roční 13.3% a 29%, resp. Pokud jsme ovšem porovnali takto časově standardizovanou mortalitu mezi jednotlivými léty, nenalezli jsme žádný signifikatnější trend. U pacientů, kteří byli z hospitalizace propuštěni (tj. přežili primární příhodu), věk, mužské pohlaví, předcházející CMP, fibrilace síní, vstupní zvýšená glykemie a zvýšený kreatinin predikují signifikantně zvýšení 5-ti leté mortality, zatímco léčba statinem, clopidogrelem či antikoagulancii naopak mortalitu predikují negativně (tj. působí jako „ochranné“ faktory).

4.4.3 Prediktory kvality života a její vztah k mortalitnímu riziku

Tato sub-analýza byla realizována u souboru pacientů vyšetřených v roce 2007 (EUROASPIRE-stroke survey), přičemž kvalita života (QoL) byla objektivizována pomocí skórovacího systému – dotazníku SF-36 (36-item Short-Form Health Survey) (příloha 4). Anxieta, deprese (na základě HADS skore ≥11), BNP ≥ 100 ng/mL, reziduální motorický deficit a Rankinovo skore ≥ 4 při propuštění a zvýšený krevní tlak se ukázaly jako hlavní determinanty zhoršené kvality života v průřezové analýze. V prospektivním sledování snížená kvalita života nezávisle (po komplexní asociaci) predikovala 5-tiletou celkovou či kardiovaskulární mortalitu [HRR 2.01 (95%CI:1.21-3.32), p <0.007 či 2.32 (95%CI:1.32-4.09), p<0.003, resp.)]

4.4.4 Paradoxní vztah obezity a krevního tlaku na přežívání po ischemické CMP.

Tyto sub-analýzy byly realizovány v souboru ESH stroke survey (a to včetně dat ještě z iniciální hospitalizace). Normální tělesná konstituce (BMI méně než 25) či pokles tělesné hmotnosti o 3 kg se ukázaly jako významný nezávislý ukazatel přežívání pacientů po CMP (spojený s vice než pětinásobným vzestupem mortality) časně po propuštění z hospitalizace

(tj. v průběhu prvních 16 měsíců). Naopak obezita se paradoxně ukázala jako "ochranný faktor" (příloha 5).

Podobně paradoxní vztah byl v jiné analýze nalezen směrem ke krevnímu tlaku v akutním stádiu CM/P (tj. během hospitalizace). Pacienti, jejichž střední tlak při přijetí činil 100-110 či ti, jejichž systolický tlak při propuštění byl nižší než 120, umírali po dimisi signifikatně častěji než ti s vyššími hodnotami.

4.4.5 Vztah mezi subtypem CMP a polymorfismem genu pro prothrombin

Tato subanalýza byla opět realizována na souboru pacientů ESH stroke survey a testována byla asociace mezi dvěma polymorfismy pro prothrombin (rs6025 a rs1799963) a subtypem mrtvice (tj. obstrukce velké tepny, kardioembolická CMP, lakunární CMP, nedeterminovaná CMP) stanoveným systémem CCS (Causative Classification of Stroke System). Zjištěno bylo, že kombinace polymorfismu rs1799963 a aktivního kouření je spojena s excesivním rizikem "nedeterminovaného" subtypu CMP (pravděpodobně jako důsledek excesivního trombotického rizika postižených osob) (příloha 6).

4.4.6 Vztah mezi mortalitou pacientů se stabilizovanou vaskulární chorobou a biomarkery kalcifikace cévní stěny

Tato sub-analýza byla realizována na spojeném souboru EUROASPIRE III+ EUROASPIRE III stroke survey (tj. jak pacienti po CMP, tak i s ICHS). Zaměřena byla na aditivní mortalitní riziko, spojené s tzv. matrix Gla proteinem (MGP), který je přirozeným inhibitorem vaskulárních kalcifikací a jednu, z jehož isoforem dp-ucMGP (desfosforylovaný nekarboxylovaný MGP) lze použít jako biomarker tohoto patofyziologického procesu (vaskulárních kalcifikací). Zjistili jsme, že zvýšená hodnota dp-ucMGP na úrovni 4. kvartilu byla spojena s asi dvojnásobným rizikem 5-tileté celkové či kardiovaskulární mortality (příloha 7).

5. DISKUZE

5.1 Jaká je reálná adherence k doporučeným cílům sekundární prevence ischemické CMP a jak by se situace mohla zlepšit?

Souhrnně lze na základě našich výsledků konstatovat, že klinická realita v oblasti sekundární prevence ischemické CMP má velmi daleko k tomu být optimální a skutečná adherence k doporučeným hodnotám kontroly konvenčních rizikových faktorů je mnohdy až ostudně nízká. Pokud vezmeme jeden z nejzávažnějších rizikových faktorů CMP vůbec, tedy hypertenzi, její náležité terapeutické kontroly bylo dosaženo jen u necelých 44% vyšetřených pacientů, a navíc zde není možno sledovat ani zásadnější zlešení v průběhu sledovaného období. Na tomto místě je také nutno vzít v úvahu i další nová fakta. V relativně nedávné studii SPRINT (zmíněné již v teoretickém úvodu) bylo prokázáno, že intenzivnější léčba antihypertenzívy k nižší cílové hodnotě (STK v průměru ≈121 mmHg) byla provázena u vysokorizikových subjektů (včetně pacientů s manifestní vaskulární chorobou) také o 25% nižším rizikem celkové mortality již během necelých 3,5 let léčby [91]. Jakkoliv se řadu let vedla debata o tzv. J křivce vztahu mezi dosaženým TK a rizikem MACE u pacientů s ICHS a Guidelines z roku 2016 navíc stanovují „jednotnou“ cílovou hodnotu TK < 140/90 mmHg [7]) speciálně pro incidenci cerebrovaskulárních příhod, J křivka nikdy neplatila a vztah pro tento faktor byl celkem lineární (tj. čím nižší tlak byl dosažený léčbou, tím vyšší profit z hlediska redukce CMP zde byl pozorován). Lze tedy přinejmenším důvodně spekulovat o tom, že optimální cílová hodnota TK v sekundární prevenci po ischemické CMP by se klidně mohla pohybovat až někde u 120/80 mmHg (a situace v praxi je tedy ještě horší, než co říkají naše výsledky).

Podobně „neradostná“ situace zůstává v oblasti intervence lipidového profilu, kde se zároveň cílové hodnoty léčby za posledních 20 let asi nejvíce měnily (z LDL < 3 mmol/L v roce 1998

na současných < 1.8 mmol/L) Více striktní léčebný cíl je založen především na jakési „druhé generaci“ statinových studií (tj. PROVE-IT, TNT, IDEAL, AtoZ u pacientů s ICHS, a SPARCL po ischemické CMP), které konzistentně prokázaly, že čím vyšší je použitá dávka statinu, tím vyšší je také v sekundární prevenci přínos ve smyslu redukce incidence MACE [92]. Striktní léčebný cíl LDL < 1.8 mmol/L odvozený z těchto studií (a formulovaný přinejmenším od roku 2012) však do klinické praxe proniká spíše jen „neochotně“- v našem souboru dosáhlo cílové hodnoty LDL < 1.8 mmol/L jen pouhých 14% pacientů. Nejvíce na vině je pravděpodobně dlouhodobá neochota ambulantních lékařů předepisovat statiny ve vyšší dávce (a většina pacientů by takto vyžadovala nejvyšší dostupnou dávku, tj. buď atorvastatin 80mg nebo rosuvastatin 40 mg) a také fakt, že vysokodávkovaný statin není pacientům doporučen již iniciálně (tj. v době propuštění pro primární vaskulární příhodu). V české části studie EUROASPIRE IV z roku 2012/13 užívalo nejvyšší dostupnou dávku statinu jen zcela zanedbatelných 2.4% pacientů v sekundární prevenci ICHS [93] - u pacientů po CMP se v našich souborech takovýto jedinec nevyskytl vůbec. Na druhé straně je v současné době přece jenom již znát, že preskribce vysokodávkovaného statinu roste přinejmenším u pacientů po infarktu myokardu (ve studii EUROASPIRE V z roku 2017 to již bylo až 26% pacientů) a lze doufat, že se agresivní léčba dyslipidémie promítne i mezi pacienty po ischemické CMP. K dosažení současné velmi přísné cílové hodnoty LDL máme nově alespoň teoreticky k dispozici i další terapeutické nástroje. Prvním krokem bude pravděpodobně přidání ezetimibu. Kombinace ezetimibu se středně dávkovaným statinem vedla u pacientů v sekundární prevenci ve studii IMPROVE-IT k cca 24% poklesu LDL a o necelých 7% nižšímu relativnímu riziku incidence MACE (oproti monoterapii statinem) [26]. Ezetimib je také v klinické praxi používán již řadu let a i u nás relativně ekonomicky přijatelný. Novější přístup představují inhibitory enzymu PCSK-9 (proprotein-konvertáza-subtilizin-kexin 9). Inaktivací tohoto specifického enzymu se dosáhne zvýšení exprese LDL

receptoru na povrchu hepatocytu a tím i řádového vzestupu „internalizace“ LDL částic do jater. Již registrovány (a v omezené míře i v klinické praxi) jsou dvě monoklonální protilátky proti tomuto enzymu (evolokumab, alirokumab). PCSK-9 inhibitory vykazují do té doby prakticky nevídanou hypolipidemickou účinnost, např. ve studii LAPLACE-TIMI 57 [94] byl evolokumab podáván subkutánně každé dva týdny a spojen s více než 66% poklesem LDL! Zcela recentně máme k dispozici také výsledky prvních studií v sekundární prevenci ICHS „s tvrdým výstupem“. Studie FOURIER [27] realizovaná na více než 27 500 pacientů se stabilizovanou aterovaskulární chorobou a hodnotou LDL přes 1.8 mmol/L (léčených středně- či vysokodávkovaným statinem). Léčba evolokumabem byla provázena nejen ≈ 60% poklesem LDL (podobně jako v ostatních studiích s touto látkou), ale také signifikantním 21% poklesem incidence velkých kardiovaskulárních příhod oproti placebu.

Další poměrně zásadní problematiku v sekundární prevenci představuje diabetes mellitus a další formy porušeného glukozového metabolismu. Více než 37% pacientů již bylo možno kategorizovat jako manifestní diabetiky (tj. s glykemií nalačno ≥ 7 mmol/l nebo léčbou antidiabetiky) a ještě dalších asi 16% plnilo kritéria porušené glykemie nalačno. Při podrobnější diagnostice zahrnující ještě i glykovaný hemoglobin, náležité kontroly glukozového metabolismu (tj. glykemie nalačno ≥7 mmol/l a/nebo HbA1c ≥ 48 mmol/mol) v celém souboru nedosahovalo 37.7% probandů. Přestože o roli poruchy glukozového metabolismu v etiologii aterovaskulárních chorob celkem nikdo nepochyboval, z pohledu principů „medicíny založené na důkazu“ bylo donedávna „iritující“ chybění jednoznačnějšího důkazu přínosu antidiabetické léčby z hlediska redukce rizika MACE (v kontextu diabetu označovaného jako jeho „makrovaskulární komplikace). Jakkoliv běžná antidiabetická léčba založená na inzulinu a/nebo perorálních antidiabeticích účinně snižuje glykemii i riziko rozvoje tzv. mikrovaskulárních komplikací (diabetické retino-, nefro- či polyneuropatie…) z hlediska jinak důvodně očekávatelné redukce kardiovaskulárních příhod, zůstává v lepším

případě neutrální, v horším je provázena dokonce vzestupem mortality [95]. Ještě Guidelines z roku 2012 doporučovala převážně léčbu založenou na metforminu (i když ani jeho výsledky z hlediska efektu na redukci MACE nebyly nijak oslňující) a postulovala i pojem „maximální bezpečné léčby“ diabetu (korelující s hodnotou HbA1c 48 mmol/mol). Ani novější generace perorálních antidiabetik typu DPP-4 inhibitorů nepřinesla zásadnější změnu a jejich účinek na incidenci makrovaskulárních komplikací byl převážně neutrální (což bylo eufemicky označováno jako „kardiovaskulární netoxicita“). Přelom nastal až s dvěma novými látkami. Empaglifozin (antidiabetikum typu SGLT-2 inhibitor, zvyšující močovou exkreci glukózy) byl ve studii EMPA-REG Outcomes [36] provázen nejen poklesem glykemie, ale také (konečně!) i významným 38% poklesem kardiovaskulární mortality. Podobně ve studii LEADER [37] byl liraglutid (antidiabetikum typu GLP-1 analog, zabraňující převážně postprandiálnímu vzestupu glykemie) provázen opět signifikantní 22% redukcí celkové mortality. Jakkoliv obě studie nebyly primárně designovány k průkazu efektu antidiabetické léčby v sekundární prevenci, lze jejich výsledky do určité míry extrapolovat i na pacienty s manifestní aterovaskulární chorobou.

5.2 Jaká je situace v oblasti péče v akutním stádiu CMP a další farmakoterapie v sekundární prevenci?

V této oblasti lze najít jak příznivé, tak i méně příznivé zprávy. Dobrou zprávou je bezesporu to, že proporce iniciální hospitalizace na iktové jednotce stoupla mezi lety 2007 a 2012/13 více než šestinásobně, zatímco proporce iniciální trombolýzy dokonce vice než devítinásobně. Je prokázané, že centralizace péče po iCMP do podoby “iktových center” zrychluje všechny nezbytné kroky v kritické časné fázi po iCMP a vede i ke zmírnění následků iCMP [96,97]. Na druhé straně indikace trombolýzy byla v plzeňském centru v roce 2012/13 stále ještě o vice než 60% častější než v pražském, přestože na iktové jednotce bylo hospitalizováno pacientů zhruba podobně. Tento rozdíl zřejmě odráží zkušenost s tímto typem léčby, která je v

plzeňském centru delší než v Praze 5 (kde ještě v době první studie centralizovaná péče i trombolýzy poskytovány nebyly vůbec). Lze předpokládat, že pro většinu pacientů v České republice (mimo velké aglomerace) bude ale reálná dostupnost centralizovaná péče v podobě iktové jednotky a propracované metodiky časného managementu spíše omezená a hrubě determinovaná dojezdovou dobou mezi bydlištěm a takto specializovaným centrem. Existují také data dokazující, že bezprostřední přínos z hlediska poklesu mortality byl pozorován pouze v nemocnicích, kde existuje definovaný a centralizovaný „protokol" v časném přístupu iCMP, ve srovnání se zařízeními poskytujícími pouze obvyklou péči [96]. Vybudování dostatečně kapacitní a hlavně v krátkém časovém intervalu dostupné sítě, navíc obsazené vyškolenými týmy zdravotníků a poskytujícími tak časnou péči po CMP podle recentních standardů, je úkol pro tvůrce zdravotní politiky a bude jistě vyžadovat ještě řadu let.

Antiagregační léčba představuje základní opatření u všech typů aterovaskulárních chorob a spolu s antikoagulační léčbou byla v našem souboru preskribována asi u 87-93% pacientů. Na druhou stranu, převážná většina pacientů byla stále léčena pouze monoterapií aspirinem. Ze studie CHARISMA [65] přitom vyplynulo, že monoterapie clopidogrelem vykazovala u pacientů s cerebrovaskulární chorobou superioritu oproti monoterapii aspirinem. Naopak duální antiagregace clopidogrel *plus* aspirin (obvyklá u ICHS) se ukázala méně bezpečná než monoterapie clopidogrelem, při prakticky stejné účinnosti [66] - právě v souvislosti s výsledky této studie byla již v roce 2008 upravena doporučení v tomto směru [98]. V naší studii však bylo v roce 2012/13 léčeno clopidogrelem pouze 18% pacientů. Toto nízké číslo lze ale vysvětlit tím, že v době propuštění z hospitalizace (cca 2011-12) nebyl ještě clopidogrel u nás plně hrazen zdravotními pojišťovnami v indikaci sekundární prevence iCMP a klinická realita se v dalších letech poměrně zásadně zlepšila (podle jiných našich dat byl clopidogrel předepsán při propuštění z hospitalizace u 48% pacientů). Alternativní

dvojkombinace antiagregancií, tj. aspirin *plus* dipyridamol byla užívaná v roce 2012/13 pouze 6 pacienty, a to nejspíše z důvodů špatné subjektivní tolerance pacienty.

K zásadnímu přelomu by mohlo dojít v oblasti fibrilace síní (FIS). Ta, ač není nejčastěji zastoupeným rizikovým faktorem CMP, etiologicky představuje asi nejrobustnější a nejvíce rizikový parametr. Prevalence permanentní fibrilace či flutteru síní činila v našich souborech asi 12%. Tato hodnota však spíše podceňuje reálnou situaci (pravděpodobně kvůli tomu, že náš soubor zahrnoval relativně nízkorizikové pacienty po CMP- viz dále) a v jiném našem neselektovaném souboru pacientů po CMP činila prevalence FIS až 25% (velké registry udávají i více než 33% [99]). V každém případě až 24% z našich vyšetřených pacientů neužívalo žádnou antikoagulační léčbu a k tomuto počtu je třeba připočíst ještě jistě nezanedbatelné množství osob s nezachycenou paroxysmální formou FIS, podle aktuálních principů rovněž již indikovaných k antikoagulační léčbě. Takto zásadní množství pacientů neužívajících antikoagulační léčbu (a hrubě tak vystavených riziku recidivy CMP) by se ale v příštích letech mohlo snížit díky rozmachu nových antikoagulancií, slibujících přinejmenším stejnou antitrombotickou účinnost, ale zejména vyšší bezpečnost z hlediska hemorhagických mozkových příhod a dalších krvácivých komplikací [100]

5.3 Proč a nakolik se liší v praxi realizace sekundární prevence a další osud pacientů po ischemické CMP a po infarktu myokardu?

Je vcelku evidentní, že prodělaná CMP determinuje osud pacienta zásadně jinak, než je tomu v případě infarktu myokardu. Na prvním místě je nutno asi zmínit značně vyšší mortalitní riziko u pacientů po CMP. V naší studii, ač jsme porovnávali v podstatě jen velmi dobře stabilizované jedince a iniciálně bezpochyby ty s méně mutilujícím průběhem choroby, bylo pětileté mortalitní riziko pacientů po iCMP více než 2.7x vyšší (28.5% *versus* 9.5%). Jiná naše mortalitní analýza, zahrnující takřka 10 000 pacientů hospitalizovaných ve FN Plzeň pro

infarkt či CMP (avšak tentokrát všechny a nikoliv jen ty, kteří přežili alespoň 6 měsíců po akutní příhodě), ukázala zhruba podobný rozdíl v pětileté mortalitě (22.1% versus 49.5%). Navíc je nutno vzít v úvahu, že i výsledný funkční stav po CMP je nesrovnatelně horší než po infarktu myokardu, ať již hlediska kvality života, celkové funkční kapacity, ale třeba i výskytu deprese a dokonce i srdečního selhávání (logicky spíše očekávatelného v případě infarktu). Důvodů tohoto zásadního rozdílu je celá řada. Z těch neovlivnitelných je to především fakt, že k CMP dochází spíše ve vyšším věku, kdy riziko dalších komplikací a komorbidit je přece jenom také zvýšené (rozdíl průměrného věku našich souborů činil pouze necelých 5 let, ale to je dáno také tím, že věk probandů byl uměle „zastropován“).

Druhým, spíše jen z části a velmi těžko ovlivnitelným důvodem je obecná dostupnost (či spíše existence) péče v nejakutnějším stádiu. Pacienti s infarktem myokardu jsou dnes obvykle transportováni záchrannou službou přímo do spádového kardiocentra a v naprosté většině (podle našich dat až v 95 procentech) podstoupí diagnostickou koronární angiografii a přinejmenším pokus o revaskularizaci myokardu. Možnosti akutní léčby v případě ischemické CMP jsou zcela nesrovnatelně horší. Především je zde časová bariéra, kdy se řada pacientů (většina?) velmi rychle ocitne mimo „terapeutické okno“, a to jak vlastní vinou, tak i vlivem neovlivnitelných okolností (např. CMP během spánku). Fyzickou bariéru představuje dojezdová vzdálenost do centra poskytujícího příslušnou specializovanou péči. Jakkoliv se u nás v průběhu posledních let mnoho v této oblasti dosti zásadně změnilo, jedná se převážně o zlepšení terapeutických procesů v rámci příslušného centra a bohužel nikoliv rozšíření jejich možností pro výrazněji vyšší množství pacientů s CMP.

Posledním zásadním důvodem, tentokrát (alespoň teoreticky) relativně snadno ovlivnitelným, může být celkový přístup k příslušným pacientům. Pacienti po infarktu myokardu profitují nejen z propracované medicínské technologie v akutním stavu choroby, ale i péče v sekundární prevenci je celkem dobře institucionalizovaná a pacient se pravděpodobně

dlouhodobě dostane „do rukou“ kardiologa či jiného lékaře se zkušeností s daným typem péče. Naopak pacient po CMP se po propuštění z hospitalizace ocitá jaksi „ve vzduchoprázdnu“. Není jasné, kdo se má péčí o takového pacienta konkrétně zabývat- může to být internista, neurolog, kardiolog, ale jak vyplývá z našich dat s největší pravděpodobností to bude nakonec „jen“ praktický lékař (jehož zaměření musí být poměrně zásadně extenzivnější, tudíž specializovanější přístup po něm lze jen těžko požadovat a např. v preskribci je navíc mnohdy uměle omezován). Evidentním důsledkem je (a to vyplývá i z našich výsledků), že principy sekundární prevence jsou do praxe u nás stále poměrně málo implementovány.

5.4 Limitace studie

S ohledem na design primárních surveyí (EUROASPIRE, ESH Stroke Survey) naše analýza zahrnuje převážně dobře stabilizované pacienty, vyšetřené minimálně 6 měsíců po kardiovaskulární příhodě (≈1 roku v mediánu) navíc s pravděpodobně relativně příznivým průběhem onemocnění (nejtěžší pacienti zemřeli během hospitalizace či ještě před vyšetřením, event. nebyli schopni se k němu dostavit) a dobře realizovaným úvodním managementem (více než 95% bylo po koronární revaskularizaci). Lze tedy předpokládat, že z eventuální intervence ve smyslu např. antidepresivní léčby by ještě byly schopni profitovat. Pokud vezmeme v úvahu reprezentativnost výsledků, je nutné si také uvědomit, že se jedná o pacienty „nakupené“ v oblasti větších aglomerací a zejména v relativní blízkosti velkých zdravotnických center (pacienti bydlící dále než 50 km od příslušeného centra již vzhledem k předpokládaným problémům s dopravou nebyli primárně zváni). Lze tedy předpokládat, že výsledky od pacientů z „okrajovějších“ oblastí naší republiky mohou být odlišné (resp. nejspíše ještě daleko horší)

6. SOUHRN A ZÁVĚRY PRO PRAXI

- Péče o pacienty v akutní fázi CMP (tj. během hospitalizace) se v posledních 10 letech zcela jednoznačně zlepšila.
- Posun k lepšímu je vidět z hlediska preskribce základní farmakoterapie s prokázaným účinkem v sekundární prevenci CMP. Na druhé straně z hlediska náležitého rozsahu tato léčba zůstává daleko svému optimu a je obecně spíše poddávkovaná.
- Globální kontrola konvenčního rizikového profilu zdaleka nedosahuje svého plného potenciálu, což částečně může přispívat k vysokému mortalitnímu riziku (a to v případě jinak dobře stabilizovaných pacientů po ischemické CMP).
- Zásadní limity zůstávají v oblasti organizace dlouhodobé péče o tyto pacienty.
- Nejvyšší potenciál ke snížení globálních zdravotních, sociálních i ekonomických dopadů cerebrovaskulárních chorob si stále udržuje primární prevence (a reálně nelze očekávat, že by se na tom mohlo v příštích letech cokoliv změnit).

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Original research article

The changes of secondary prevention practice in Czech post-stroke patients between 2007 and 2012/13

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ABSTRACT

It is evident that post-stroke patients benefit from appropriate secondary prevention; however, in clinical reality these patients are often overlooked in these terms. We aimed to evaluate the changes in adherence to treatment targets (defined by current guidelines) since 2007 in Czech patients after first ischemic stroke.

Two independent descriptive surveys were undertaken in 2007 and 2012/13. Consecutive patients less than 81 years of age suffering for verified first ischemic stroke were identified and examined at least 6 months afterwards.

The study population included 2 series of 341 and 424 patients, aged 69.0 (±SD 9.1) and 66.8 (±SD 10.4) years, respectively. The initial stroke management improved between 2007 and 2012/13, the proportion of patients initially hospitalized at stroke unit raised significantly from 6.5 to 41.8%, while initial thrombolysis from 2.4 to 22.2%. Prescription rate of statins increased from 52.2 to 62.0%, while of clopidogrel from 0 to 18.4%.

In 2007 survey about 39% of patients were obese, 61% showed inappropriate blood pressure, 68% were hypercholesterolemic and 33% had inappropriate glucose control. Over time, only control hypercholesterolemia significantly improved between 2007 and 2012/13 (proportion of patients with LDL ≥2.5 mmol/L decreased from 67.9 to 58.3%).

In 2007 survey we observed particularly high mortality risk. 5-year all-cause mortality and cardiovascular mortality were 25.8% and 19.9%, respectively.

In conclusion, despite substantial improvement in acute management, clinical practice in secondary prevention in post-stroke patients remains far from being optimal.

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Introduction

The ultimate goal of treatment of patients with atherovascular disease is to reduce the case fatality, risk of recurrent cardiovascular event, extend life-time and improve its quality. Management of patients with coronary heart disease (CHD) was defined extensively by the series of Joint European Societies' Guidelines since 1994 [1–5], and since the third revision of these guidelines [3], effective prevention in patients with established cerebrovascular disease (i.e. post-ischemic stroke) has also been defined as priority. Similar principles (as in coronary heart disease patients), including treatment target value of conventional cardiovascular risk profile and several "mandatory" pharmacotherapies, should be adopted for clinical practice.

To describe the clinical reality in secondary prevention of CHD with respect to adherence to these guidelines, the EUROASPIRE (European Action on Secondary Prevention by Intervention to Reduce Events) project was started with repeated surveys on patients with clinically manifest CHD that were realized in 1995/96, 1999/2000, 2006/7 and finally in 2012/13 (i.e. EUROASPIRE I–IV projects) [6–9]. Data of these surveys demonstrated high prevalence of inadequately controlled modifiable risk factors and insufficient prescription of basic pharmacotherapies in secondary prevention of CHD across all European countries included. The comparable data in patients with cerebrovascular disease were generally lacking until a stroke-specific module was developed as voluntary add-on to the EUROASPIRE III survey. The aims and objectives of this module were to identify prevalence of CHD risk factors, lifestyle habits and medication use among patients after first ischemic stroke in order to describe the current status of clinical practice against Third European Guidelines principles and this survey was realized in four European countries (five EUROASPIRE project centers) in 2007 [10], including Czech Republic [11]. The stroke-specific module of EUROASPIRE III study demonstrated that basic secondary prevention principles were implemented into real clinical practice in post-stroke patients in even less extent, than in CHD patients. The results highlighted the need for structured disease management and targeted secondary prevention strategies after stroke. Second survey in patients with cerebrovascular disease (ESH Stroke survey) was started in 2012 (and currently analyzed) under the nearly similar protocol [12] and in the same Czech centers as EUROASPIRE III survey in 2007.

The aim of present analysis is to demonstrate the changes in clinical practice in secondary prevention of cerebrovascular disease between 2007 and 2012/13 in Czech centers of above mentioned surveys.

Materials and methods

Study population and study design

The study population consists of Czech patients examined in the framework of two well-defined surveys in patients after first ischemic stroke, EUROASPIRE III – stroke specific module in 2007 and ESH stroke survey in 2012–13. The selection of study subject and protocol of examination were virtually similar for both surveys and described in detail elsewhere [10–12]. Both surveys were conducted in two centers in Czech Republic: University Hospital Pilsen and the Centre for Cardiovascular Prevention of Thomayer's Hospital in Prague.

Patients with the diagnosis of ischemic stroke were identified from hospital discharge lists. Stroke was defined according to the World Health Organization criteria [13] and ischemic etiology of stroke was verified by brain imaging (either CT or MRI scan). Patients with recurrent stroke event (previous transient ischemic attack was acceptable), secondary hemorrhagic transformation, aged more than 80 years at the time of index event, patients not living in the study region and those who deceased during index (stroke) hospitalization were excluded. The recruitment was done by reviewing hospital records retro-consecutively (i.e. starting with the most recent stroke hospitalization backwards until the planned pool of ~500 patients was reached). Finally, in first survey (2007) 507 patients met inclusion criterion (i.e. first verified ischemic stroke), but of them 77 died after discharge from index hospitalization – i.e. 430 patients were finally invited for interview. In the second survey (2012–13) 736 patients met inclusion criteria, with 162 after-discharge deaths, i.e. 574 patients were invited.

Clinical examinations

Interview was realized at least 6 months after admission for index stroke event, during single (about 3 months) campaign. Information on personal and demographic characteristics, personal and family history of coronary heart disease, lifestyle and pharmacotherapy was obtained. The following clinical examinations were performed: height and weight were measured in light indoor clothes without shoes using SECA 220 scales and measuring sticks. Waist circumference was measured using a steel tape measure. Blood pressure (BP) was measured twice in the sitting position on the right arm using a standard mercury sphygmomanometer (and the average value was used). Current (i.e. at time of interview) evident neurological deficit (aphasia, facial palsy, limb paresis or several sensitive deficit) was assessed by the examiner (physician specialized in internal medicine), while the global disability was considered using Barthel ADL (activities of daily living) Index [14]. A standard 12-channel ECG was obtained in all patients and the presence of atrial fibrillation was considered by examiner. Breath carbon monoxide was measured by a SMOKERLYSER device (model EC 50, Bedfont Scientific, Upchurch, UK) to verify the reported smoking habit.

Biochemical examination

Venous blood samples were drawn after at least 12 h of overnight fasting. All laboratory examinations were performed in series from aliquots stored at −70° and included: estimation of serum total (TCHOL) and HDL (HDL) cholesterol, using an ARCHITECT c800 analyzer (Abbott Laboratories, Germany) and DOT Diagnostics commercial kits (Czech Republic); the same analyzer was used for measuring serum triglycerides (TG) and glucose (GLU). HbA1c was estimated by ionex liquid chromatography using G7 analyzer (TOSOH, Japan). LDL was calculated

by Friedewald equation, i.e. LDL = TCHOL – HDL – (TG/2.22) when TGs ≤4.5 mmol/L.

Data analysis

Two independent samples (i.e. data obtained at interviews) were compared by non-paired manner. Moreover, we ascertained the vital status of 2007 survey patients through May 31, 2012 using National mortality registry of Czech Institute for Medical Information and Statistics. We used ICD-10 codes in death certificates to specify the cause of death. These data were used for prospective mortality analysis. The mortality (censoring) data are available for all patients. Power calculations revealed that our population of patients was sufficiently large to estimate the expected 5-year mortality rate with 5% relative precision.

Conventional risk factors were dichotomized by usual target values according to the 3rd/4th Joint European Guidelines [3,4] (see relevant section of tables). A patient was labeled as "current smoker" if he/she self-reported it or had a carbon monoxide in breath value exceeding 10 ppm at the time of interview, while "persistent smoking" means proportion of current smokers to all those smoking at time of stroke. Presence of dysplasia at interview, facial palsy or limb paresis at interview was considered as "residual neurologic impairment", while only limb paresis was considered as "residual motoric impairment". For statistical analyses, we used STATISTICA 8 and STATA/SE 8 software. Standard statistical methods were used, i.e. Mann–Whitney U test, χ^2 test, multiple linear regression and Cox proportional hazard regression.

Results

Characteristics of participants

A total of 341 and 424 patients after first verified ischemic stroke, with mean age 69.0 (±SD 9.1) and 66.8 (±SD 10.4) years, respectively, were interviewed in the course of first (2007) and second (2012–13) surveys and compared in the present analysis. Excluding patients, who died between discharge from hospitalization for stroke and interview, the overall respondence to interviews was 79.3% and 73.9%. The baseline characteristics and current functional (neurological) status at interview, and some details on initial management at time of stroke manifestation are given in Table 1.

Control of risk factors

Risk factors categorized with respect to 3rd/4th Joint European Guidelines targets are given in Table 2 (i.e. non-adherence in % of patients exceeding the target value is depicted). Only prevalence of hypercholesterolemia significantly dropped between 2007 and 2012/13 in our series, while prevalence of increased waist circumference increased significantly.

Basic secondary prevention pharmacotherapy is also given in Table 2. The prescription rate of clopidogrel raised from zero

Table 1 – Baseline cross-sectional characteristics of the study samples and risk profile at time of interview.

	2007	2012–13	p-Value[b]
n	341	424	–
Gender [% of males]	58.9	60.6	0.64
History of transient ischemic attack [%]	4.4	4.3	0.14
Concomitant coronary heart disease[a] [%]	14.4	10.8	0.92
Initial hospitalization in stroke unit [%]	6.5	41.8	<0.0001
Initial thrombolysis [%]	2.4	22.2	<0.0001
At interview:			
Age [years]	69.0 (9.1)	66.8 (10.4)	0.007
Median time (interquart. range) between stroke Manifestation and interview [years]	1.58 (0.94–2.39)	1.36 (0.86–2.38)	0.06
Barthel Index	92.4 (8.7)	96.1 (10.2)	<0.0001
Any neurological deficit [%]	31.7	55.0	<0.0001
Residual motoric deficit [%]	24.9	39.4	<0.0001
Permanent atrial fibrillation [%]	13.8	11.4	0.32
Current smoking [%]	15.8	23.8	0.006
Body mass index [kg/m^2]	29.1 (5.0)	29.1 (5.0)	0.24
Waist circumference [cm]	100.2 (12.8)	98.8 (13.5)	0.22
Systolic blood pressure [mmHg]	143.2 (21.0)	142.2 (22.6)	0.35
Diastolic blood pressure [mmHg]	84.5 (11.1)	83.0 (12.3)	0.023
Total cholesterol [mmol/L]	5.11 (1.12)	4.90 (1.21)	0.002
LDL cholesterol [mmol/L]	3.02 (0.97)	2.81 (1.01)	0.001
HDL cholesterol [mmol/L]	1.39 (0.39)	1.37 (0.37)	0.54
Triglycerides [mmol/L]	1.58 (0.80)	1.61 (1.05)	0.33
Fasting glucose [mmol/L]	6.81 (2.60)	6.59 (2.13)	0.59
Hemoglobin A1c [mmol/mol]	45.1 (12.1)	44.8 (11.0)	<0.0001

[a] History of myocardial infarction or coronary revascularization.
[b] Mann–Whitney U test for continuous variables, χ^2 test for categorical variables

Table 2 – Adherence to target values for secondary prevention and treatment used in both surveys [%].

	2007	2012/13	p for trend
Smoking			
Current smoking[a]	15.8	23.8	0.029
Persistent smoking after stroke[b]	62.5	63.6	0.91
Overweight			
BMI ≥ 25 kg/m^2	81.4	82.4	0.66
BMI ≥ 30 kg/m^2	38.8	42.0	0.44
Increased waist circumference[c]	58.4	82.1	<0.0001
Raised blood pressure			
SBP ≥ 140 *and/or* DBP ≥ 90 mmHg	60.7	56.6	0.37
SBP ≥ 180 *and/or* DBP ≥ 110 mmHg	10.9	13.2	0.34
Dyslipidemias			
TCHOL ≥ 4.5 mmol/L	69.5	60.5	0.014
LDL ≥ 2.5 mmol/L	67.9	58.3	0.010
LDL ≥ 1.8 mmol/L	89.3	85.6	0.13
HDL < 1^m or 1.2^f mmol/L	53.0	49.8	0.58
TG ≥ 1.7 mmol/L	30.8	29.7	0.48
Impaired glucose metabolism			
Overt diabetes[d]	34.0	37.5	0.24
Impaired fasting glucose[e]	21.6	16.3	0.06
Fasting glucose ≥ 6.1 mmol/L	52.4	48.2	0.31
Fasting glucose ≥ 7 mmol/L	29.0	27.5	0.77
Fasting glucose ≥ 7 mmol/L *and/or* HbA1c ≥ 48 mmol/mol	32.8	37.7	0.11
Reported treatment			
Antiplatelets [%]	70.1	76.6	0.08
Antiplatelets or anticoagulants [%]	86.2	92.0	0.009
Aspirin	67.2	57.3	0.003
Clopidogrel monotherapy	0	18.4	–
Aspirin *plus* dipyridamole	2.9	3.3	0.81
Any antihypertensives [%]	88.3	84.0	0.54
ACEIs or ARBs [%]	68.9	70.5	0.55
Thiazide diuretics	22.3	25.7	0.14
Any lipid-lowering drugs [%]	55.4	63.9	0.013
Statins [%]	52.2	62.0	0.004
Any antidiabetics [%]	22.3	20.8	0.76

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TCHOL, total cholesterol; TG, triglycerides; ACEIs, angiotensin converting enzyme inhibitors; ARBs, angiotensin receptor blockers.

[a] Self-reported or >10 ppm of carbon monoxide in breath.

[b] Proportion of current smokers to all those smoking at the time of stroke.

[c] ≥102 cm in males and ≥88 cm in females.

[d] Fasting glucose ≥7 mmol/L or treatment with antidiabetics.

[e] Fasting glucose 6.1–6.9 mmol/L but no treatment with antidiabetics. [m]males; [f]females.

p-Value adjusted for age and gender.

Table 3 – 5-year mortality hazard risk ratios of risk factors and treatments in 2007 survey.

	All-cause mortality		Cardiovascular mortality	
	HRRs (95% CI)	p	HRRs (95% CI)	p
Age ≥65 years	3.15 (1.73–5.71)	<0.001	2.84 (1.49–5.43)	0.002
Male gender	1.10 (0.69–1.75)	0.68	0.98 (0.58–1.65)	0.92
Obesity[a]	0.80 (0.48–1.35)	0.40	0.77 (041–1.45)	0.42
Increased waist circumference[b]	0.91 (0.53–1.55)	0.72	0.61 (0.33–1.11)	0.10
Current smoking[c]	1.36 (0.75–2.46)	0.31	1.17 (0.59–2.33)	0.65
Raised blood pressure[d]	0.67 (0.45–0.99)	0.12	0.72 (0.44–1.18)	0.19
LDL cholesterol ≥2.5 mmol/L[e]	0.81 (0.49–1.31)	0.39	0.85 (0.49–1.50)	0.58
Inappropriate glycemic control[f]	1.96 (1.24–3.10)	0.004	1.93 (1.14–3.26)	0.014
Treatment with statin	0.92 (0.58–1.46)	0.73	1.06 (0.62–1.79)	0.84
Treatment with ACEIs or ARBs	1.07 (0.67–1.73)	0.77	1.05 (0.61–1.78)	0.87

HRRs, hazard risk ratio from Cox proportional hazard models, all covariates listed in table.

[a] Body mass index ≥30 kg/m^2.

[b] Waist circumference ≥94 cm in males and ≥80 cm in females.

[c] Self-reported or >10 ppm of carbon monoxide in breath.

[d] Systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg.

[f] Fasting glucose ≥7 mmol/L and/or HbA1c ≥48 mmol/mol.

to about 18%, and moreover, significant increase was found also in statin prescription.

Mortality follow-up analysis

During median follow-up of 1959 days (5.4 years), 97 patients interviewed in the first survey (2007) deceased (28.5%), and 75 of these fatal events were considered cardiovascular. The corresponding 5-year all-cause mortality and cardiovascular mortality were 25.8% and 19.9%, respectively. We further analyzed the dichotomized conventional risk factors and treatments as 5-year mortality predictors using a multivariable adjusted Cox model (Table 3). Only age over 64 years and inappropriate glycemic control (defined as fasting glucose ≥7 mmol/L and/or HbA1c ≥48 mmol/mol) were identified as significant predictor of all-cause or cardiovascular mortality.

Discussion

Our study consisted of two independent samples of stable patients after first ischemic stroke. The key aim was to validate the changes in secondary prevention practice in post-stroke patients over 5–6 years in Czech Republic, i.e. never analyzed and published data in our population.

Changes in acute stroke management

It is evident that centralization of stroke care into stroke units improved and speeds up management in critical early phase of stroke and leads also to more favorable outcomes [15–17]. In the present study we observed that proportion of initial management on stroke unit increased over time between 2007 and 2012 more than 6-fold, while rate of initial thrombolysis was more than 9-fold. On the other hand, the thrombolysis rate in Pilsen center in 2012/13 was more than 60% higher than in Prague center, in spite that proportion of initial management on stroke units was nearly similar. This probably reflects longer experience with this type of treatment – stroke care was centralized into stroke unit several years earlier in Pilsen area than in Prague 5 (in 2007 were both, stroke unit-care and thrombolysis provided only in Pilsen center). We may also presume that for huge proportion of Czech stroke patients outside of large agglomerations, currently initial centralized stroke management is virtually unavailable. It has been reported that mortality benefit of initial stroke care was observed only in hospitals with dedicated stroke service (i.e. specialized stroke units and developed early rapid management), in contrast to hospitals providing only stroke wards and standard stroke management protocols [17]. Thus, building an efficient network of specialized stroke centers with the skilled teams and multi-level management is the commission for health policy makers and will probably still claim several years.

Changes in risk profile control

The equivocal perspective we observed also considered trends in secondary prevention practice. Favorable trends were observed in control of hypercholesterolemia. LDL concentrations significantly decreased in average and target LDL concentration is now being achieved by ~ 41% of all patients. Moreover, statin prescription increased from 52 to 62%. On the other hand, recent 5th Joint European Guidelines [5] lowered the target to LDL <1.8 mmol/L in all patients with manifest vascular patients, including those post-ischemic strokes. This new target is based on very convincing evidence [18] in patients with coronary heart disease, but most likely transferable into mortality benefit even in secondary prevention of cerebrovascular diseases (post-stroke). In 2012/13, only about 14% of patients reached this new target LDL <1.8 mmol/L in our series. To get this new target in the wide scale, the use of aggressive dosage regimen of statins will be substantial. In our sample, about 89% of statin-treated patients used only (sub) standard dose of atorvastatin 20 mg or equivalent (appropriate more for primary, than for secondary prevention). Only 6.4% of all patients are treated with at least moderate statin dose (atorvastatin 40 mg or equivalent) and only one subject was treated with 80 mg of atorvastatin. Surprisingly, up to 38% of patients in 2012/13 survey were without any statin treatment! This is strongly against current guidelines [5], recommending statin treatment in all patients with manifest atherovascular disease independently of its localization, age or other covariates. The efficacy of high-dose statin in the setting of 4731 patients after stroke or TIA was proved in SPACL study [19]. Treatment with 80 mg of atorvastatin was followed by 84% relative reduction of recurrent stroke or 80% reduction major cardiovascular events, compared to placebo. Based on SPARCL results, the guidelines were updated and intensive statin treatment is now being recommended in all post-stroke or TIA patients [20]. Thus, inappropriate statin treatment (e.g. under-dosed or even non-existent) represents major unused potential to improve the secondary prevention practice in post-stroke patients.

Management of hypertension remained also generally sub-optimal. Recommended target blood pressure reached in only less than 40% of patients in 2007 and trends to improvement over time was minimal (~43%). Overall, blood pressure represents the most important risk factor of stroke, and treatment with antihypertensive drugs was associated with significant reductions in recurrent strokes. Meta-analysis of 7 interventional studies in 15,527 post-stroke patients is showing the significant 34% decrease of recurrent stroke relative risk, or 31% decrease of any vascular event incidence risk [21]. The impact of blood pressure reduction was similar in the patients with hypertension and when all subjects, including those without hypertension, were analyzed. Moreover, significant reductions in recurrent stroke were seen with diuretics alone and in combination with angiotensin converting enzyme inhibitors (ACEIs) but not with β-blockers or ACEIs monotherapy. In the present study, the prescription rate of ACEI or angiotensin receptor blockers remained virtually unchanged over time between 2007 and 2012 (~69% versus 71%), while prescription of diuretics or combination of both decreased as far as ~40% versus 30%, or 30% versus 27%, respectively. Based on current evidence [21,22], these drug classes seems be the most appropriate in secondary prevention after ischemic stroke and in our opinion should be used in nearly all our patients, excluding perhaps only those with clear normotension or symptomatic post-treatment hypotension.

Antiplatelets or anticoagulants were prescribed in ~87–93% of patients in both surveys. However, majority of patients on antiplatelets were treated with aspirin monotherapy only. It is evident from CHARISMA trial [23] that clopidogrel monotherapy was in patients with cerebrovascular disease superior to aspirin monotherapy. In contrast, only monotherapy with clopidogrel was in patients with cerebrovascular disease equally efficient, but safer than clopidogrel *plus* aspirin combination [24]. In concert with these findings the guidelines for secondary prevention in post-stroke patients in 2008 were updated [20]. In reality, only 18% of patients were treated with clopidogrel in our 2012–13 survey. We may speculate that this rather low rate is caused by fact that at the time of interview (2012) clopidogrel was not yet fully covered by Czech Health Insurance system for indication of post-stroke secondary prevention and that this will keep improving currently and in the near future. Another evidence-based antiplatelet combination, aspirin *plus* dipyridamole was used in 6 patients only in 2012, probably because of its well clinically known and evident inferior tolerance [23].

The important question is whether the situation in Czech Republic differed from other European countries. The problem is that adherence to secondary prevention targets was not yet systematically audited in European-wide scale. We are only able to compare the Czech data with other countries involved in EUROASPIRE III – stroke specific module [10] in 2007 (i.e. Croatia, Germany and Poland). Generally, there were no substantial differences in adherence to secondary prevention targets between these countries. Prevalence of patients with raised blood pressure was slightly different in Czech centers only, than in Croatia, Germany and Poland (≈61% versus 65%, 57% and 64%, respectively), while control of hypercholesterolemia (defined as TCHOL >5 mmol) was significantly less strict in Czech centers, i.e. ≈60.3% versus 47%, 47% and 57%, respectively ($p = 0.01$). More-than-less marginal differences were observed also in prescription rate of basic pharmacotherapies (statins, antihypertensives, antiplatelets/anticoagulants) [10]. For similar reasons (e.g. missing systematic data) we are not able to compare the trends in Czech Republic to the rest of Europe, or these data are only anecdotal. For example, in large survey of post-stroke patients from Lombardy region (Italy) it was observed that the prescription rate of lipid-lowering drugs increased over six-year period by about 8–9% (i.e. nearly similar than in our centers), but in fact, the prescription rate in 2010 was substantially lower (≈35%) than our survey [25].

Mortality analysis

The second part of our study was mortality analysis of 2007 survey. Overall, the mortality of our subjects was rather high, despite of its relative stable condition at the time of interview. All-cause total 5-year mortality was ca 28%, giving more than 5% per-year mortality. Comparing with Czech patients with stable coronary heart disease (post-myocardial infarction and/or coronary revascularization), evaluated in EUROASPIRE study, the 5-year mortality risk in post-stroke patients was more than 2.7-fold higher (28.5% versus 9.5%) [9]. In addition, despite these high mortality rates in our analysis, evaluated sample represents paradoxically less affected post-stroke patients, because the most severely ill subjects died between discharge from hospital and interview (~ 20%) or even immediately at stroke manifestation.

Among conventional risk factors and treatments with evident benefit in secondary prevention, only poor glycemic control (defined as fasting glycemia ≥7 mmol/L and/or HbA1c ≥48 mmol/mol) entered (beside age) the regression model as independent 5-year all-cause mortality predictor. The prevalence of type 2 diabetes or prediabetic disorder (impaired fasting glucose) were very high (~54–56%) and suboptimal control of diabetes were found in both surveys (33% and 38% in 2007 and 2012 surveys, respectively).

Study limitations

Our study involved only patients initially included and accumulated around large (university) hospitals. Therefore we may speculate that clinical reality in secondary prevention of post-stroke patients outside of large agglomerations might be even worse, because of relatively more complicated availability of specialized health care. Our series also consisted without any doubt of relatively less-affected post-stroke patients. Most complicated patients died before interview and we can speculate that the majority of living non-responders did not attend the interview because of very poor general health condition (immobility, need permanent institutionalization in nursing house, etc.). On the other hand, the fact that our series involved less-affected patients with still existing potential for secondary prevention, should strengthen practical utility of our results. We have also no data about non-fatal vascular events, namely stroke recurrences.

Conclusions

Management of stroke in acute phase substantially improved since 2007. Prescription rate of basic pharmacotherapy with evident benefit in post-stroke patient also increased, but still remains far from its optimum and used drugs are generally under-dosed. Similarly, in spite of improvement in single risk factors (namely lipids), the global control of risk profile remains generally inappropriate and corresponding mortality risk of post-stroke patients remains very high.

Conflict of interest

None declared.

Ethical statement

All procedures performed in this study were in accordance with the Good Clinical Practice principles and ethical standards formulated in the 1964 Declaration of Helsinki and its later amendments. The local Ethics Committees of the University Hospital in Pilsen and Institute of Clinical and Experimental Medicine approved of the study protocols. The data were stored and evaluated under the provisions of the Czech Data Protection Act.

Informed consent

All study participants agreed voluntarily to participate in the research project and signed the Informed consent form.

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Original Research

A comparison of secondary prevention practice in poststroke and coronary heart disease patients

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ABSTRACT

Objectives: It is evident that patients with atherosclerotic vascular disease (AVD) benefit from appropriate secondary prevention. In clinical reality, the secondary prevention in AVD patients other than those with coronary heart disease (CHD) is often overlooked. Therefore, we compared the adherence to secondary prevention principles between poststroke and CHD patients.

Study design: Descriptive (cross-sectional) study with prospective mortality follow-up.

Methods: We examined 1729 chronic patients with AVD (mean age 65.9 (±SD 9.6) years), 964 with CHD, and 765 poststroke (pooled data of Czech samples of EUROASPIRE III, IV, and the ESH stroke survey). The interview was performed 6–36 months after the coronary event/revascularization or the first ischemic stroke, while the mortality follow-up 5 years after this interview.

Results: Poststroke patients had a significantly higher risk of persistent smoking, blood pressure ≥140/90 mmHg and LDL ≥2.5 mmol/L than CHD patients [odds ratios adjusted for age, gender and survey were 1.63 (95% CI: 1.13–2.33), 1.38 (95% CI: 1.13–1.69) and 2.26 (95% CI: 1.84–2.78), respectively]. In contrast, poststroke patients showed a lower risk of inappropriate glucose control and hypertriglyceridemia [0.66 (95%CI: 0.54–0.82) and 0.74 (95%CI: 0.61–0.91), respectively]. The prescription rates of antiplatelets/anticoagulants, antihypertensives and statins were also significantly lower in poststroke than in CHD patients (89.4 vs 93.7, 85.9 vs 97.5, and 57.7 vs 89.8, respectively).

Mortality analysis was performed in a subsample of 815 subjects interviewed in 2006/07. The 5-year all-cause mortality rates were 25.8% and 13.3% in poststroke and coronary

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patients, respectively ($P = 0.0023$); the hazard ratio for stroke adjusted for major risk factors was 1.85 (95% CI: 1.31–2.63).

Conclusions: Compared to CHD patients, poststroke patients are strongly handicapped in terms of poor adherence to secondary prevention target, prescription of basic pharmacotherapies and mortality risk.

Introduction

The ultimate goal of treatment of patients with atherosclerotic vascular disease (AVD) is to reduce the case fatality, to reduce risk of recurrent cardiovascular event, to extend lifetime, and to improve life quality. Management of patients with coronary heart disease (CHD) was defined extensively by the series of Joint European Societies' Guidelines since 1994.[1–5] Since the third revision of these Guidelines,[3] also patients with AVD in non-coronary localisations (including those after ischemic stroke) have been included in the group with highest priority for prevention. To implement secondary prevention measures in poststroke patients in clinical practice, we should adopt similar principles as those applicable to CHD patients, i.e. strictly defined treatment targets for major cardiovascular risk factors, several 'mandatory' pharmacotherapies, and necessary lifestyle changes.

To describe clinical reality in secondary prevention of CHD with respect to adherence to these guidelines, the EUROASPIRE (European Action on Secondary Prevention by Intervention to Reduce Events) survey was conducted in 1995/96 (EUROASPIRE I),[6] to be subsequently repeated in 1999/2000, 2006/7 and in 2012/13 (i.e. EUROASPIRE II-IV, respectively).[7–9] Data from these surveys demonstrated a high prevalence of inadequately controlled modifiable risk factors and insufficient prescription of basic pharmacotherapies in the secondary prevention of CHD across all European countries included.

Comparable data regarding patients with cerebrovascular disease were virtually non-existent until the stroke-specific module was developed as a voluntary add-on to the EUROASPIRE III survey. The objective of this module was to identify the prevalence of CVD risk factors, lifestyle habits, and medication use among patients after their first ischemic stroke in order to describe the current status of clinical practice against the Third European Guidelines principles. This survey was performed in four European countries (five EUROASPIRE project centres) in 2007,[10] including the Czech Republic.[11] The Stroke Specific Module of the EUROASPIRE III study highlighted the need for structured disease management and targeted secondary prevention strategies. A second survey in patients with cerebrovascular disease (ESH Stroke Survey) was started in 2012 (and currently analyzed) under the nearly similar protocol[12] and in the same Czech centres as the EUROASPIRE III survey in 2007.

The aim of the present analysis is to demonstrate the differences in clinical practice in secondary prevention between poststroke and CHD patients and the corresponding mortality outcomes using data from EUROASPIRE III, IV and ESH stroke survey from 2006/07 and 2012–14.

Methods

Study population

The study population consists of Czech patients examined in the framework of well-defined surveys in patients with CHD or in patients after their first ischemic stroke. Patients with CHD represent pooled Czech samples of the EUROASPIRE III (2006/07) and IV (2013/14) surveys, while poststroke patients represent pooled Czech samples of the EUROASPIRE III-stroke survey (2006/07) and ESH stroke survey (2012/13); the selection and standard protocol of examination (nearly similar for all four surveys) have been described in detail elsewhere.[8–12] All four surveys were conducted in two centers in the Czech Republic: the University Hospital Pilsen and the Centre for Cardiovascular Prevention of Thomayer Hospital in Prague.

CHD patients[9] aged ≤80 years hospitalized for any of the following discharge diagnosis were retrospectively identified from hospital records: first coronary artery bypass graft (CABG), first percutaneous transluminal coronary angioplasty (PTCA), and acute myocardial infarction or ischemia. Recruitment of patients started with the most recent hospital record and proceeded backwards until the required sample of 600 subjects was achieved. The interview of patients was performed 6–36 months after the index event (coronary event or revascularization).

The poststroke patients were selected in the same manner.[11,12] A sample of at least 500 (at least 700 in the second survey) consecutive patients aged ≤80 years hospitalized for their first ischemic stroke was selected and the responders were interviewed.

Clinical examinations and biochemical measurements

Information on personal and demographic characteristics, personal and family history of CHD, lifestyle and self-reported pharmacotherapy were obtained at the interview. The following clinical examinations were performed: height and weight were measured in light indoor clothes without shoes using SECA 220 scales and measuring sticks (SECA GmbH & Co, Hamburg, Germany). Waist circumference was measured using a steel tape measure. Blood pressure (BP) was measured in the sitting position after at least 5 min rest on the right arm using a standard mercury sphygmomanometer and appropriate cuff. Generally, blood pressure value reported in this

paper represents the average of two readings taken 5 min apart. However, if the difference between two readings was more than 10 mmHg, additional readings were done (and the average calculated from last two values). Breath carbon monoxide was measured by a SMOKERLYSER device (model EC 50, Bedfont Scientific, Upchurch, UK) to verify the reported smoking habit.

Standard protocol for blood sampling and sample handling was followed. Venous blood samples were drawn after at least 12 h of overnight fasting. Centrifugation of blood samples was done at 3500 rpm for 10 min after at least 30 min in room temperature (to ensure that the blood had clotted), but no longer than 60 min. Immediately after centrifugation, the serum, plasma or erythrocytes were separated to aliquots and stored at −80 °C. Laboratory examinations included: estimation of serum total (TCHOL) and HDL (HDL) cholesterol using an ARCHITECT c800 analyzer (Abbott Laboratories, Wiesbaden, Germany) and commercial kits (DOT Diagnostics, Prague, Czech Republic); the same analyzer was used for measuring serum triglycerides (TG) and glucose (GLU), whereas HbA1c was estimated from erythrocytes by ionex liquid chromatography using an G7 analyzer (TOSOH, Shunan, Japan). All these examinations were done in the Department of Clinical Biochemistry and Hematology of University Hospital Pilsen. The laboratory has been accredited by Czech Accreditation Service and fulfills the requirements of the ISO standards, including routine quality control.

Data management

Two independent samples (data obtained at interviews) were compared in a non-paired manner (CHD patients vs poststroke patients) in cross-sectional part of our analysis. To analyzed 5-year mortality, we ascertained the vital status of patients undergoing the interview in 2006/07 (i.e. EUROASPIRE III and EUROASPIRE III-stroke survey) using the National Mortality Registry of the Czech Institute for Medical Information and Statistics. We obtained exact date of death and in deceased subjects the reported cause of death. We used ICD-10 codes in death certificates to specify the cause of death. The mortality (censoring) data were available for all patients.

Conventional risk factors were dichotomized by usual target values according to the Third/Fourth Joint European Guidelines[3,4] (see relevant section of tables). A patient was labeled as a 'current smoker' if he/she self-reported it or had a carbon monoxide in breath value exceeding 10 ppm at the time of interview, while 'smoking persistence' means the proportion of current smokers to all those smoking at the time of index hospitalization (i.e. acute coronary syndrome, coronary revascularization or stroke).

Power calculation was done to estimate sample sizes necessary for demonstrating differences in prevalence (factor proportion) of 5%, 10% and 20% (based on a two-sided test with 80% power resent)- a sample size of 400 patients in each group was found enough to detect differences of at least 10%. Similarly, power calculation for prospective analysis revealed that our population of patients was sufficiently large to estimate the expected 5-year mortality rate with a 5% relative precision at the 95% confidence level.

For statistical analyses, we used STATISTICA 8 and STATA/SE 8 software. Statistical analysis was performed using standard methods, i.e. descriptive statistic, Mann–Whitney U test or χ^2 test and multiple logistic regression. Moreover, for the purpose of mortality analysis we used the Mantel–Cox log-rank test and the Cox proportional hazard model.

Results

Characteristics of participants

A total of 1729 patients, 765 patients after their first verified ischemic stroke and 964 with manifest CHD, with a mean age of 67.8 (±SD 9.9) and 64.3 (±SD 9.0) years, respectively, were compared in the present analysis. After exclusion patients who deceased between the index event and the survey, the overall response rates to interviews by inclusion diagnosis were 76.2% and 86.3%, respectively (for details see flow chart on Fig. 1). The baseline characteristics of interviewed subjects are shown in Table 1. Poststroke patients were significantly older and more frequently women, had higher systolic blood pressure, total, LDL and HDL cholesterol, while significantly smaller waist circumference, lower triglycerides, fasting glucose and HbA1c concentrations. Poststroke patients were significantly less frequently followed by the specialist (neurologist or cardiologist) than CHD patients. In CHD patients the proportion of coronary revascularization procedures (either PTCA or CABG) was 95.2%, while among poststroke patients the proportion of carotic revascularization (carotic endarterectomy or angioplasty; prior or after event) was only 5.2%. Out of 264 patients with atrial fibrillation, 94.2% of CHD and 62.5% of poststroke patients received anticoagulants (data not in Table).

Basic pharmacotherapies and adherence to treatment targets

Poststroke patients were significantly less frequently treated with antiplatelets or anticoagulants, all antihypertensive and lipid-lowering drugs (namely with statins, Table 1).

Table 2 gives the prevalence of risk factors dichotomized according to the Third/Fourth Joint European Guidelines targets (i.e. showing non-adherence in percentage of patients exceeding the target value) and adjusted odds ratios for inadequately controlled risk factors in poststroke compared to CHD patients. Poststroke patients were more often persistent smokers, had larger waist circumference, inadequately controlled blood pressure, and hypercholesterolemia, while the prevalence of hypertriglyceridemia and inappropriate controlled glycaemia was less frequent compared to CHD patients.

Furthermore, we analyzed the risk of inadequately controlled risk factors in poststroke patients in subgroups of major covariates (i.e. age, gender and year of survey, Table 3). A significantly higher risk of raised blood pressure in poststroke patients (compared to CHD patients) was found in males, patients younger than 65 years and those interviewed in the second survey (2012–14). In contrast, control of hypercholesterolemia was poorer in poststroke patients than in

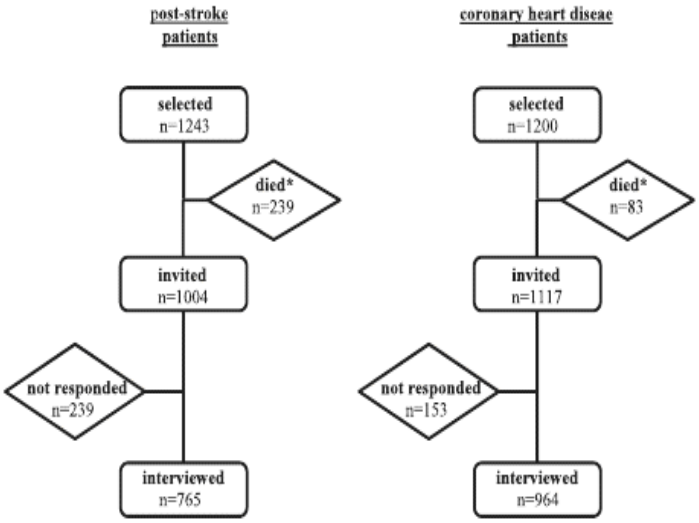

Fig. 1 – Flow chart of sample recruitment process. *deceased between discharge from hospitalization for stroke or coronary heart disease manifestation and the time of study interview.

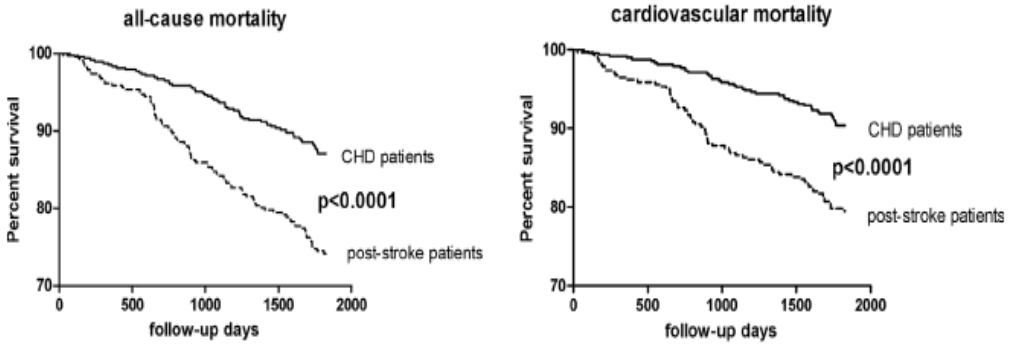

Fig. 2 – Kaplan–Meier survival curves for all-cause and cardiovascular mortality in stable poststroke and CHD patients (P value by Mantel–Cox test).

CHD patients, specifically in those older than 65 years and those interviewed in the first survey (2006/07).

Mortality follow-up analysis

Mortality analysis was performed in 815 subjects with a mean age of 65.3 (±SD 9.4) years (70.2% of patients were males) interviewed in the course of the first survey (2006/07) (see Fig. 2). During median follow-up of 2050 days (5.6 years), 168 patients deceased (20.6%), of which 126 (15.5%) of events were considered as cardiovascular. The corresponding 5-year all-cause mortality rates were 25.8% vs 13.3% in poststroke and CHD patients, respectively ($P = 0.0023$ by the χ^2 test), while the 5-year cardiovascular mortality rates were 19.9% vs 9.7%, respectively ($P = 0.013$). Significant differences in mortality rates were found already one year after interview [total mortality: 4.1% vs 1.6% in poststroke and CHD patients, respectively ($P = 0.031$ by the χ^2 test); cardiovascular mortality: 3.8% vs 1.0%, respectively ($P = 0.0069$)].

Fig. 1 shows the Kaplan–Meier survival curves. Stroke as an inclusion diagnosis was associated with significantly poorer survival in terms of both – all-cause or cardiovascular mortality. Using a multivariate Cox model and after complex adjustment for dichotomized conventional risk factors (Table 4), stroke was associated with a significant 85% risk increase of all-cause mortality and 89% risk increase of cardiovascular mortality. Adding of the treatment with statins, antidiabetics and angiotensin-converting inhibitors or angiotensin II receptor blockers in the same regression model did not change these results (corresponding adjusted hazard ratios for stroke were 1.78 (95% CI: 1.24–2.55) and 1.83 (95% CI: 1.19–2.77) for all-cause and cardiovascular mortality, respectively).

Discussion

To our best knowledge, this study is the first to compare directly the adherence to treatment targets between poststroke and CHD patients in secondary prevention. The key

Table 1 – Baseline cross-sectional characteristics of samples of poststroke and CHD patients and reported pharmacotherapies at interview [mean (standard deviation) or factor proportion].

	Pooled data	Poststroke patients	CHD patients	P
n	1729	765	964	–
age [years]	65.9 (9.6)	67.8 (9.9)	64.3	<0.0001
gender [% of males]	70.7	59.9	79.4	<0.0001[b]
time to interview [years]	1.44 (0.77)	1.69 (0.91)	1.24 (0.56)	<0.0001
% of patients in 1st survey[a]	47.1	44.6	49.2	0.057[b]
Risk factors:				
current smoking [%]	19.6	20.3	19.1	0.55[b]
body mass index [kg/m^2]	29.4 (4.8)	29.3 (5.3)	29.4 (4.4)	0.12
waist circumference [cm]	101.7 (12.9)	99.4 (13.2)	103.5 (11.6)	<0.0001
systolic blood pressure [mmHg]	141.5 (20.8)	142.7 (21.9)	140.6 (19.9)	0.021
diastolic blood pressure [mmHg]	83.6 (11.5)	83.7 (11.8)	83.6 (11.4)	0.65
total cholesterol [mmol/L]	4.71 (1.20)	5.00 (1.17)	4.49 (1.18)	<0.0001
HDL cholesterol [mmol/L]	1.28 (0.34)	1.38 (0.38)	1.20 (0.29)	<0.0001
LDL cholesterol [mmo/L]	2.66 (0.95)	2.91 (1.00)	2.46 (0.87)	<0.0001
triglycerides [mmol/L]	1.74 (1.36)	1.59 (0.94)	1.89 (1.57)	<0.0001
fasting glucose [mmol/L]	6.96 (2.36)	6.69 (2.35)	7.17 (2.35)	<0.0001
HbA1c [mmol/mol]	44.1 (12.2)	43.9 (11.6)	44.2 (12.7)	0.53
self-reported pharmacotherapy:				
antiplatelets [%]	81.8	73.7	88.2	<0.0001[b]
anticoagulants [%]	10.6	17.0	5.5	<0.0001[b]
any antihypertensives [%]	92.4	85.9	97.5	<0.0001[b]
thiazide diuretics or indapamide [%]	19.8	24.2	16.4	<0.0001[b]
ACEi or ARB [%]	74.6	69.8	78.4	<0.0001[b]
any hypolipidemics [%]	76.7	60.1	89.8	<0.0001[b]
statins [%]	75.5	57.7	89.8	<0.0001[b]
any antidiabetics [%]	23.5	21.4	25.2	0.066[b]
heath care providing physician:				
cardiologist or neurologist	61.4	40.3	78.1	<0.0001[c]
other internal medicine specialist	7.4	12.9	3.0	
general practitioner only	31.2	46.8	18.9	

CHD, coronary heart disease; ACEi, angiotensin converting inhibitors; ARB, angiotensin II receptor blockers.

[a] Interview realized in 2006/07.

[b] P value by Mann–Whitney U test for continuous or by χ^2 test for categorized variables.

[c] Proportion of subcategories by χ^2 test.

Table 2 – Non-adherence to treatment-target values of conventional risk factors in coronary and poststroke patients.

	Risk factor proportion [%]		OR (95%CIs)[a]	P[b]
	Poststroke patients	Coronary patients		
smoking persistence[c]	63.2	51.8	1.63 (1.13–2.33)	0.008
body mass index ≥30 kg/m^2	40.6	39.7	0.98 (0.78–1.20)	0.082
increased waist circumference[d]	71.4	62.9	1.25 (1.01–1.55)	0.042
raised blood pressure[e]	58.4	50.7	1.38 (1.13–1.69)	0.002
LDL cholesterol ≥2.5 mmol/L	62.7	42.5	2.26 (1.84–2.78)	<0.0001
low HDL cholesterol[f]	51.2	33.8	1.55 (1.23–1.95)	<0.0001
Triglycerides ≥1.7 mmol/L	30.2	42.1	0.66 (0.54–0.82)	<0.0001
inappropriate glycemic control[g]	35.6	40.8	0.74 (0.61–0.91)	<0.0001

OR, odds ratio; CI, confidence intervals.

[a] odds ratio of risk factor presence in poststroke patients (if in CHD patients equal to 1), adjusted for age, gender and year of survey (2006/07 *versus* 2012–14).

[b] P value adjusted for above mentioned factors.

[c] proportion of current smokers to all those smoking at time of index hospitalization for coronary event or stroke; ≥ 102 cm in males and ≥88 cm in females.

[d] waist circumference ≥ 102 cm in men or ≥ 88 cm in women.

[e] systolic blood pressure ≥140 and/or diastolic blood pressure ≥90 mmHg.

[f] HDL <1.0 mmol/L in males or <1.2 mmol/L in females.

[g] fasting glucose ≥7 mmol/L and/or HbA1c ≥48 mmol/mol.

Table 3 – Odds ratios of non-adherence to treatment-target values of poststroke patients (versus CHD patients) in subgroups by major covariates.

	Persistent smoking[a]		Body mass index ≥30 kg/m^2		Raised blood pressure[b]		LDL ≥2.5 mmol/L		Inappropriate glycemic control[c]	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
Age										
<65 years	1.63 (1.03–2.57)		1.01 (0.74–1.37)		1.55 (1.13–2.11)		2.00 (1.45–2.75)		0.85 (0.61–1.17)	
≥65 years	1.76 (0.96–3.23)	0.62	1.23 (0.94–1.61)	0.07	1.19 (0.91–1.55)	0.004	2.73 (2.08–3.58)	0.002	0.77 (0.59–0.99)	0.036
Gender										
males	1.79 (1.17–2.75)		1.01 (0.79–1.29)		1.52 (1.20–1.94)		2.29 (1.79–2.93)		0.76 (0.59–0.97)	
females	1.30 (0.65–2.60)	0.89	0.92 (0.64–1.33)	<0.001	1.09 (0.75–1.59)	0.010	2.29 (1.57–3.34)	0.87	0.71 (0.49–1.03)	0.99
Year of survey										
2006/07	1.87 (1.03–3.41)		1.05 (0.77–1.44)		0.82 (0.60–1.11)		2.58 (1.88–3.55)		0.79 (0.58–1.08)	
2012–14	1.54 (0.97–2.44)	0.42	0.96 (0.74–1.26)	0.055	2.06 (1.56–2.70)	<0.001	2.12 (1.60–2.80)	0.001	0.75 (0.57–0.99)	0.037

Multiple logistic regression [odds ratio (95% confidence interval); if in CHD patients equal to 1].
P values for interaction are in italic (significant if lower than 0.05).
[a] Proportion of current smokers to all those smoking at time of index hospitalization for coronary event or stroke.
[b] systolic blood pressure ≥140 and/or diastolic blood pressure ≥90 mmHg.
[c] fasting glucose ≥7 mmol/L and/or HbA1c ≥48 mmol/mol.

finding of our study is that the practical implementation of secondary prevention principles, in terms of appropriate control of conventional cardiovascular risk factor, is markedly poorer in poststroke patients than in CHD patients (despite that these principles are almost the same). Poststroke patients are also at substantially higher mortality risk than CHD patients even after adjustment for individual levels of conventional risk factor control.

Adherence to secondary prevention principles

Blood pressure represents the most important risk factor of stroke not only in primary prevention but also in secondary prevention. Indeed, treatment with antihypertensive drugs was associated with reduction of stroke recurrence.[13] In the prevention of recurrent stroke, the use of diuretic alone[14] or in combination with angiotensin-converting enzyme inhibitors (ACEi)[15] was beneficial, but not the use of β-blockers, calcium antagonists or ACE/angiotensin II receptor blockers monotherapy (ARB).[13] Based on our findings the adherence to blood pressure target (<140/90 mmHg) is far from being optimal in both CHD and poststroke patients (50.7 and 58.4% of patients did not have their blood pressure controlled). However, even after adjustment for age, poststroke patients were at significantly higher risk (by 38%) of non-adherence to blood pressure target than CHD patients. Poststroke patients were less often treated with antihypertensives that CHD patients (~86% vs 98%). Moreover, diuretics alone or in combination with ACEi/ARB were prescribed in only 24.2% and 20.0% of poststroke patients. Our data also showed that antihypertensive pharmacotherapy was under-dosed. In addition to that, we observed that relative difference in blood pressure control between CHD and poststroke patients increased over time between 2006/07 and 2012/14 (Table 3). However, this phenomenon was not caused by the worsening of hypertension control in poststroke patients but by the improvement in CHD patients.

The level of the control of hypercholesterolemia was similar to control of hypertension. Target LDL concentration was achieved in ~37% of the whole sample of poststroke patients and only moderate improvement was observed over time between the 2006/07 and 2012/14 surveys (adherence to target LDL value <2.5 raised from 32.1% to 41.7%). After adjustment for major confounders, poststroke patients were at more than two-fold higher risk of inappropriately controlled hypercholesterolemia. This difference can be probably accounted for substandard prescription of statins in poststroke patients compared to CHD patients (~58% vs 90%). In addition, SPARCL trial[16] clearly demonstrated that poststroke patients benefit from high-dose statin (atorvastatin 80 mg or equivalent). Moreover, a series of trials in CHD patients confirmed that high-dose statin was followed with higher mortality/morbidity reduction that standard-dose statin,[17] and it is generally accepted that these results can be extrapolated to non-coronary AVD patients (including poststroke patients). Therefore, the recent Guidelines[5] adopted a new, more stringent LDL target <1.8 mmol/L for all patients with any type of AVD. In our series, only one poststroke patient was treated with 80 mg of atorvastatin in 2012–14 survey and only ~14% of patients were adherent to the new LDL target (<1.8 mmol/L).

Table 4 – 5-years mortality hazard risk ratios of stroke as initial diagnosis and risk factors control as covariates in 2006/07 surveys.

	All-cause mortality		Cardiovascular mortality	
	HRRs (95% CI)	P	HRRs (95% CI)	P
stroke as inclusion diagnosis	1.85 (1.31–2.63)	0.001	1.89 (1.26–2.84)	0.002
age≥ 65 years	2.92 (1.97–4.32)	<0.0001	3.06 (1.93–4.87)	<0.0001
male gender	1.33 (0.92–1.91)	0.13	1.20 (0.80–1.82)	0.38
current smoking	1.14 (0.73–1.79)	0.57	1.00 (0.58–1.73)	0.99
body mass index ≥30 kg/m^2	0.86 (0.61–1.21)	0.38	0.71 (0.47–1.07)	0.10
raised blood pressure[a]	0.80 (0.57–1.10)	0.17	0.88 (0.60–1.28)	0.50
LDL cholesterol ≥2.5 mmol/L	0.80 (0.57–1.12)	0.20	0.83 (0.56–1.23)	0.35
inappropriate glycemic control[b]	1.43 (1.03–2.00)	0.034	1.42 (0.97–2.09)	0.073

HRRs, hazard risk ratios from Cox proportional hazard model.
[a] systolic blood pressure ≥140 and/or diastolic blood pressure ≥90 mmHg.
[b] fasting glucose ≥7 mmol/L and/or HbA1c ≥48 mmol/mol.

Smoking cessation represents probably the most effective measure in secondary prevention with respect to mortality or recurrence of ischemic event.[18] Current smoking habit was nearly the same in CHD and poststroke patients (around 20%) due to lower smoking prevalence in poststroke patients prior to their stroke manifestation. In fact, the risk of smoking persistence after stroke manifestation was significantly higher (by 63% after adjustment for age, gender, and survey) than after CHD manifestation.

In contrast to the other major risk factor, the prevalence of diabetes or impaired fasting glycemia was significantly lower in poststroke than in CHD patients (35.9% vs 47.2% and 18.7% vs 23.7%, respectively). The treatment target for impaired glucose metabolism derived from the recent Guidelines[5] as fasting glycemia <7 and HbA1c <48 mmol/mol was reached in poststroke patients significantly more often than in CHD patients (35.6% vs 40.8%, respectively; with adjusted odds ratio for inappropriate glycemic control 0.76). It is evident that diabetes mellitus represents a major risk factor for all types of AVD. It is responsible for almost 11% of cardiovascular mortality.[19] Likewise, the relative risk of stroke incidence is more than two-fold higher in diabetic patients than in non-diabetic subjects.[20] On the other hand, it is rather unclear how to practically manage glycemic control in the secondary prevention of AVD including poststroke patients. In fact, currently there is no antidiabetic compound which enables strict glycemic control with proved efficacy on reduction of cardiovascular risk and with an appropriate safety profile in terms of acceptable risk of hypoglycemia.[21]

Furthermore, the present study showed that poststroke patients were substantially less frequently followed by a specialist (neurologist or cardiologist) than CHD patients. Indeed, approximately 48% poststroke patients were treated by general practitioners. This fact probably reflect more-than-less non-institutionalized poststroke care in Czech Republic and perhaps one of crucial reasons of generally poor adherence to secondary prevention principles.

Our data also revealed the fact that prescription rate of conventional pharmacotherapies used in secondary prevention (e.g. statins, clopidogrel, etc.) in poststroke patients is suboptimal. To our opinion, the major reason might be that these drugs are not prescribed at time of discharge from stroke hospitalization. For example, statins at the time of discharge were prescribed only in 37.9% of poststroke patients (not in Results) and this number increased by only 20% in outpatient care. We may also speculate that several poststroke patients did not tolerate the usual pharmacotherapy from various objective reasons. Bushnell and colleagues found in a prospective study that ~34% of patients discontinued at least one secondary prevention medication within one year of discharge from stroke hospitalization by healthcare provider instructions (i.e. not by self-decision).[21]

The crucial question is whether there is any real trend for improvement of secondary prevention practice in poststroke patients since the first comprehensive guidelines for stroke care (i.e. acute care and long-term management) were stated in Europe and United States.[22,23] A large survey realized in 1392 US hospitals and involving more than 1,000,000 patients after cerebrovascular event confirmed that early management and hospital outcomes dramatically improved between 2003 and 2009.[24] Similar beneficial trend in early management of stroke were observed in Czech Republic between 2006 and 2012 (Vanek et al., unpublished data). However, the adherence to secondary prevention principles improved only negligibly. Indeed, only prescription of statins and control of hypercholesterolemia improved significantly over time.

Mortality analysis

The second part of our study was analysis of mortality in the 2006/07 survey. Overall, the mortality of poststroke patients was high, despite patients' relatively stable condition at the time of interview; all-cause 5-year mortality of poststroke patients was ~26%, giving more that a 5% per-year mortality rate. Compared with the similarly stable CHD patients (post myocardial infarction and/or coronary revascularization), the 5-year mortality risk in poststroke patients was more almost double (25.8% vs 13.3%). Moreover, even after adjustment for major confounders, the mortality risk in poststroke remained by 85% higher than in CHD patients. We may only speculate about the reasons of this additive mortality risk associated with the poststroke status. First, higher age of poststroke patients is probably associated with a higher rate of comorbidities, both cardiovascular and non-cardiovascular ones. Both groups also markedly differed in terms of initial management

in the acute phase of a vascular event (stroke or acute coronary syndrome). An overwhelming majority of CHD patients (more than 95%) had re-vascularization either by PTCA or CABG as part of management during their initial hospitalization. In contrast, initial thrombolysis as only a causal treatment in the acute phase of stroke was performed in only 2.4% of poststroke patients interviewed in the 2006/07 survey. Therefore, the course of poststroke patients is more 'natural' (e.g. uninfluenced by medical management) that this after acute coronary syndrome.

Study limitations

Our study involved only patients initially included and actually treated in large (university, catchment) hospitals. We may only speculate that the clinical reality in the secondary prevention in patients outside of large agglomerations may be even worse because of the relatively more complicated availability of specialized health care.

Our series included probably less afflicted patients, and this may be presumably more pronounced in poststroke patients. The most complicated patients died before interviews and we can speculate that major part of living non-responders did not attend the interview because of their very poor general health condition (immobility, need of permanent institualization in a nursing house, etc.). To our opinion, this bias probably reflects also the fact, that overall response rate was slightly lower in poststroke than in CHD patients (76% vs 86%, respectively). Thus, the real difference between these two groups may be even higher, namely in terms of mortality risk.

Despite that, both stroke and coronary heart disease have atherosclerotic origin, their etiology markedly differs in several aspects (namely, the thromboembolism is particularly pronounced in stroke incidence risk). Therefore, in the present analysis we compared only those principles of secondary prevention, which are identical for poststroke and CHD patients. Moreover, the relative importance of each factors in terms of mortality risk or vascular event recurrence in stroke and CHD are not equivalent. Our study is also not adequately powered to analyze the data (namely the mortality outcomes) from point-of view of stroke subtype.

Conclusions

Secondary prevention management in poststroke patients in terms of adherence to recommended treatment targets are generally sub-optimal and, in several aspects (specifically control of hypertension and hypercholesterolemia) markedly worse than in CHD. There is a great potential for improvement by appropriate prescribing of basic pharmacotherapies (namely statins). Poststroke patients are definitely at very high absolute mortality risk, even when compared with CHD patients.

Author statements

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Ethical statement

The study was carried out according to the guidelines for Good Clinical Practice. The study protocols were approved by the central Ethical Committee of Institute for Clinical and Experimental Medicine, Prague and local Ethical Committee of University Hospital Pilsen. All of the participants gave written informed consent. The data were stored and evaluated under the provisions of the Czech Data Protection Act.

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Competing interests

There are no conflicts of interest to disclose.

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Original Article

Blood pressure control and risk profile in poststroke survivors: a comparison with the general population

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Objective: Recurrent strokes are associated with higher mortality, greater disability, and increased healthcare costs compared with first-ever stroke. Lifestyle measures and drug treatment in secondary prevention decrease the risk of recurrence while improving the quality of life of patients. The objective of this study was to determine the prevalence of hypertension and other cardiovascular risk factors in stroke survivors and population controls.

Methods and results: A total of 424 poststroke survivors (aged 66.0 ± 10.4 years) were examined 6–36 months after their first ischemic stroke. Controls of similar age and from the same geographic region were selected from the database of the Czech post-Multinational MONItoring of trends and determinants in CArdiovascular disease Study. Hypertension was found to be the most prevalent risk factor affecting 91.5% of stroke survivors and 71.8% of controls. Use of antihypertensive drugs was reported in 79.5% of stroke survivors and 56.7% of controls. However, blood pressure lower than 140/90 mmHg was achieved in only 49.5% of hypertensive stroke survivors. More than 60% of stroke survivors used statins but low-density lipoprotein-cholesterol lower than 2.5 mmol/l was achieved in only 47.4 and 37% of male and female poststroke survivors, respectively. About a third of poststroke patients continue to smoke, and obesity is a major problem, particularly in women (prevalence 47%), who also have a high prevalence of diabetes.

Conclusion: We found a high prevalence and poor control of major cardiovascular risk factors in patients surviving their first-ever ischemic stroke, thus showing poor implementation of guidelines for secondary prevention in clinical practice.

Keywords: anticoagulants, antiplatelets, goal blood pressure, goal low-density lipoprotein cholesterol, guidelines implementation, lipid-lowering drugs, secondary prevention in poststroke patients, smoking, stroke recurrence

Abbreviations: ACE, angiotensin-converting enzyme; ASA, acetylsalicylic acid; BP, blood pressure; CHD, coronary heart disease; ESH, European Society of Hypertension; LDL, low-density lipoprotein; OR, odds ratio

INTRODUCTION

Cerebrovascular disease is the second leading cause of death worldwide [1], and all projections indicate that this will remain so in the year 2030 [2]. Stroke is also the leading neurologic cause of long-term disability [3]; with aging of the population, a further increase in stroke incidence is expected thus causing a further burden on the population.

Stroke recurrence constitutes a quarter of all strokes [4], and recurrent strokes are associated with higher mortality, greater disability, and increased healthcare costs compared with first-ever stroke [5]. The risk of recurrence is reported to be about 16% in the first year, being about 4% in subsequent years. A history of ischemic stroke is associated with an increased risk of developing coronary heart disease (CHD). In about half of cases, stroke recurrence can be considered a failure of secondary prevention. Lifestyle measures and drug treatment in secondary prevention, possibly complemented by interventions (e.g. carotid endarterectomy), decrease the risk of recurrence while improving the quality of life of patients. Combining multiple approaches for secondary prevention of vascular events after stroke may result in a relative risk reduction by 80% [6].

Whereas there are relatively robust data on secondary prevention in CHD patients [7], data on secondary prevention in stroke survivors are scarce [8]. That was why the European Society of Hypertension (ESH) decided to conduct the ESH Stroke Survey.

The aim of this study was to determine the prevalence of hypertension and other cardiovascular risk factors in stroke survivors and population controls. Another aim was

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to analyze factors associated with controlled and uncontrolled hypertension. The data in stroke survivors were collected within the ESH Stroke Survey in the Czech Republic.

METHODS

Study population

All consecutive patients hospitalized from May 2009 to January 2012 for their first-ever ischemic stroke in Thomayer Hospital in Prague, or Charles University Hospital in Pilsen, Czech Republic, were identified retrospectively from the respective hospital databases. Both hospitals have departments of neurology with a stroke unit admitting patients with acute stroke and serving up to 280 000 inhabitants each. Stroke definition was consistent with the original WHO criteria [9], that is, symptoms lasting more than 24 h unless thrombolysis was performed, and only patients in whom computed tomography or MRI had excluded hemorrhagic stroke were eligible for inclusion. Patients aged more than 81 years or not living permanently in the study region were also excluded. A total of 736 patients (425 men, 311 women, all Caucasians, mean age 65.7 ± 10.5 years; range 22–80 years) admitted for acute stroke were found to be eligible for the study.

Hospital medical records were checked to obtain the following information: personal history of cardiovascular risk factors and disease, stroke and its intervention, data regarding the diagnostic procedures, treatment, functional outcome, and discharge. The Causative Classification of Stroke System, a computerized algorithm of the original Stop Stroke Study-Trial of Org 10172 in Acute Stroke Treatment classification [10], was used to categorize the ischemic stroke subtype by two blinded certified physicians. The National Institutes of Health Stroke Scale was used to quantify stroke severity on admission.

A total of 128 patients died during hospitalization for acute stroke or between their discharge and follow-up visit scheduled at least 6 months and no later than 3 years after acute admission for stroke.

Of the 608 surviving patients, 424 attended the follow-up visit (response rate, 69.7%) including collection of their demographic data, history of cardiovascular risk factors, atrial fibrillation, cardiovascular disease, and current drug treatment. The examination consisted of height and body weight measurement, fasting blood draw, three blood pressure (BP) measurements using a validated digital, fully automated, oscillometric device (Omron M10-IT; Omron Healthcare Co. Ltd, Kyoto, Japan) with a preformed cuff fitting medium and large arms, on the right arm (unless the affected one) in the sitting position. In patients with arrhythmias, a standard mercury sphygmomanometer (Baumanometer, W.A. Baum, Co., New York, New York, USA) with correctly sized cuffs was used. Cognitive function was assessed using the Montreal Cognitive Assessment [11]. The Hospital Anxiety and Depression Scale was used to screen patients for anxiety and depression [12]. A score of 11 or higher indicates probable anxiety or depression, whereas a score of 8–10 is considered just suggestive of a disorder.

Controls

Controls ($n = 414$) of similar age, resident in the same geographic regions as the stroke patients, were selected from a representative 1% population random sample of the Czech post-Multinational MONItoring of trends and determinants in CArdiovascular disease Study examined in 2006–2009. The overall response rate in the latest survey was 62.6%. The screening examination was performed in a similar way as the follow-up visit of stroke survivors including a physician-completed questionnaire with similar data as in stroke survivors; details have been published elsewhere [13]. BP was measured on the right arm in the sitting position, three times using a standard mercury sphygmomanometer (Baumanometer, W.A. Baum, Co.) with correctly sized cuffs.

The ESH Stroke Survey and the Czech post-Multinational MONItoring of trends and determinants in CArdiovascular disease Study were approved by the Ethics Committee of the Institute for Clinical and Experimental Medicine and Thomayer Hospital, Prague, Czech Republic. All participants provided informed consent.

Laboratory analyses

All laboratory analyses were performed in the Lipid Laboratory of the Institute for Clinical and Experimental Medicine, Prague, Czech Republic, using a fully automated enzymatic method (COBAS MIRAS analyzer, Roche Diagnostic Systems, Branchburg, New Jersey, USA) with kits of the same manufacturer. Accuracy of analysis is continuously monitored and tested by the Centers for Disease Control and Prevention (Atlanta, Georgia, USA).

Low-density lipoprotein (LDL) cholesterol was calculated using the Friedewald formula only if triglyceride levels were lower than 4.5 mmol/l (with triglyceride levels exceeding 4.5 mmol/l, LDL-cholesterol values were considered missing) [14].

Glomerular filtration rate was estimated using the equation proposed by Chronic Kidney Disease Epidemiology Collaboration [15].

Definition of major cardiovascular risk factors

Smoking was assessed using the WHO definition. A person was considered to be a current smoker if smoking at least one cigarette per day. Obesity was defined as a BMI $\geq 30\,kg/m^2$ for both sexes.

Hypertension was defined as a mean SBP ≥ 140 mmHg and/or a mean DBP ≥ 90 mmHg, or current treatment with antihypertensive medication. Treatment of hypertension was defined as current use of prescribed medication affecting BP. Hypertension control was defined as an individual receiving drug treatment for hypertension and having an SBP lower than 140 mmHg and a DBP lower than 90 mmHg.

Diabetes was defined as either fasting glycemia ≥ 7 mmol/l or treatment with oral antidiabetics and/or insulin.

Statistical analysis

Continuous variables are reported as mean $\pm$ SD or median and interquartile range. Categorical variables are reported as relative frequencies (percentage). A two-group comparison was performed by the chi-square test for categorical

variables and by Student's *t*-test for normally distributed continuous variables, and the Mann–Whitney *U* test for nonnormally distributed variables. Triglycerides were logarithmically transformed to fit the normal distribution. Two-way analysis of variance was used for simultaneous testing of the effect of sex and group for continuous variables and log-linear models were used for discrete ones. Logistic regression was used to identify factors associated with the probability of hypertension control. All tests were two-tailed and a $P < 0.05$ was considered significant. All analyses were performed using SYSTAT software version 10.0 (SYSTAT, San José, California, USA).

RESULTS

Study population characteristics

Basic characteristics of the 424 stroke survivors attending the follow-up visit at 6–36 months (median, 495 days) are presented in Table 1.

Comparison of poststroke survivors and population controls (major risk factors and drugs in secondary prevention)

Male stroke survivors were significantly younger than their female counterparts (mean age 65.9 ± 9.7 vs. 68.3 ± 11.7 years; $P = 0.020$), whereas controls were of the same age (Table 2). There were no differences in BMI between stroke survivors and population controls; also, the proportion of obese individuals (BMI ≥ 30 kg/m^2) did not differ between patients and controls.

Male poststroke patients had significantly higher SBP than controls of the same sex (143.1 ± 21.7 vs. 135.6 ± 16.7 mmHg; $P = 0.005$). Prevalence of hypertension in stroke survivors was extremely high (91.5%) as was in controls (71.7%); significantly higher in patients than in controls for both sexes. This was also applicable to the proportion of individuals being treated for hypertension. However, control of hypertension (defined as BP <140/90 mmHg) was equally poor in patients (43%) and controls (44%).

Total and LDL-cholesterol were significantly lower in stroke survivors than in controls ($P < 0.001$ for both sexes). However, the proportion of poststroke patients achieving LDL-cholesterol lower than 2.5 mmol/l was only 47.4% in men and 37.0% in women. High-density lipoprotein cholesterol was significantly lower in poststroke patients than in controls in both sexes, whereas there were no differences in triglycerides. Statins were significantly more often prescribed in stroke survivors (65% in men, 62.3% in women) than in controls ($P < 0.001$).

A significant difference in the prevalence of diabetes was found only in women (poststroke survivors 31.8% vs. controls 11.4%; $P < 0.001$). Fasting glycemia showed the same pattern ($P < 0.01$). Treatment of diabetes (either by drugs or insulin) was more common in poststroke patients ($P < 0.001$ for both sexes).

The proportion of smokers was approximately double in poststroke patients compared with controls ($P < 0.001$ for both sexes).

After eliminating the gender effect, estimated glomerular filtration rate showed a tendency toward lower values in poststroke patients; however, the proportion of individuals with limited renal function (estimated glomerular filtration rate <60 ml/min per 1.73 m^2) was higher in stroke survivors of both sexes.

Antiplatelet drugs were taken by 79.8 and 73.7% of poststroke male and female survivors, respectively. This was represented in more than 50% by low-dose acetylsalicylic acid (ASA) alone. A combination of ASA with dipyridamole was used scarcely (3.3%). Clopidogrel was prescribed in 19.5% of men and 16.8% of women surviving their first-ever ischemic stroke. Neither antiplatelet drugs nor anticoagulants were taken by 32 (7.5%) stroke survivors.

TABLE 1. Basic characteristics of stroke survivors attending follow-up visit

N	424
Men/women, *n* (%)	257/167 (60.6/39.4)
Age, years	66.0 ± 10.4
Age range, years	22.9–83.1
Education	
Basic (elementary school)	53 (12.5)
Secondary	313 (73.8)
University	58 (13.7)
Time since first-ever ischemic stroke, days	495 (315–873)
NIHSS on admission	4 (2–6)
Stroke subtype	
Large artery atherosclerosis	70 (16.5)
Cardioembolism	114 (26.9)
Lacunar	49 (11.6)
Cryptogenic	24 (5.7)
Incomplete examination	128 (30.2)
Concomitant	16 (3.8)
Other	23 (5.4)
Reperfusion therapy	
Intravenous thrombolysis	71 (16.7)
Endovascular recanalization	8 (1.9)
Intravenous thrombolysis and endovascular recanalization	3 (0.7)
Other interventions during hospitalization for acute ischemic stroke	
Carotid artery surgery	14 (3.3)
Carotid angioplasty and/or stenting	7 (1.7)
Patent foramen ovale occlusion	1 (0.2)
Hospitalization at a Stroke Unit, *n* (%)	177 (41.7)
Data from in-hospital medical records (hospitalization for acute ischemic stroke)	
History of CVD	84 (19.8)
History of risk factors	
History of hypertension	310 (73.1)
History of dyslipidemia	180 (42.5)
History of diabetes	99 (23.3)
History of atrial fibrillation	46 (10.8)
Discharge destination	
Home	345 (81.4)
Other hospital/ward	79 (18.6)
Community facility (nursing/residential home)	0
Rehabilitation unit	0
Unknown	0
Modified Rankin Scale at follow-up visit	1 (0–2)
MoCA at follow-up visit	25 (22–27)
HADS at follow-up visit	
Anxiety score	4 (2–7)
Anxiety score >8	71 (16.7)
Depression	5 (3–8)
Depression score >8	102 (24.0)

Data are presented as means ± SD, median (interquartile range) or frequency (percentage). CVD, cardiovascular disease; HADS, Hospital Anxiety and Depression Scale; MoCA, Montreal Cognitive Assessment; NIHSS, National Institutes of Health Stroke Scale.

TABLE 2. Comparison of major risk actors and drugs for secondary prevention in poststroke survivors and population controls by sex

	Poststroke survivors, men	Population controls, men	Poststroke survivors, women	Population controls, women	*P* for sex effect	*P* for effect of groups	*P* for interactions
Number	257	212	167	202			
Mean age (years)	65.9 ± 9.7	66.2 ± 4.5	68.3 ± 11.4	66.5 ± 4.5	0.020	Not significant	Not significant (0.065)
BMI (kg/m^2)	29.1 ± 4.48	28.9 ± 4.21	29.8 ± 5.74	29.7 ± 5.84	0.028	Not significant	Not significant
BMI ≥30 kg/m^2, *n* (%)	98 (38.6)	85 (40.1)	77 (47.0)	87 (43.3)	Not significant	Not significant	Not significant
SBP (mmHg)	143.1 ± 21.7	135.6 ± 16.7	136.3 ± 21.0	134.8 ± 18.5	0.005	0.001	0.030
DBP (mmHg)	83.7 ± 12.4	81.2 ± 8.8	79.4 ± 10.4	79.8 ± 10.0	0.001	Not significant	Not significant (0.054)
Hypertension, *n* (%)	241 (93.7)	155 (73.1)	147 (88.0)	142 (71.0)	Not significant	0.001	Not significant
Use of antihypertensive drugs, *n* (%)	204 (79.7)	120 (56.6)	133 (80.1)	115 (56.9)	Not significant	0.001	Not significant
BP <140/90 mmHg, *n* (%)	96 (39.8)	66 (42.6)	71 (48.3)	65 (45.8)	Not significant	Not significant	Not significant
Total cholesterol (mmol/l)	4.59 ± 1.15	5.14 ± 0.98	5.01 ± 1.18	5.39 ± 1.04	0.001	0.001	Not significant
Triglycerides (mmol/l)	1.56 ± 0.83	1.71 ± 0.09	1.52 ± 0.77	1.45 ± 0.72	0.023	Not significant	Not significant (0.095)
HDL-C (mmol/l)	1.17 ± 0.31	1.39 ± 0.34	1.41 ± 0.37	1.59 ± 0.38	0.001	0.001	Not significant
LDL-C (mmol/l)	2.72 ± 1.04	3.00 ± 0.86	2.92 ± 1.05	3.15 ± 0.98	0.013	0.001	Not significant
LDL-C <3.0 mmol/l, *n* (%)	162 (65.6)	106 (51.7)	97 (58.4)	92 (46.7)	Not significant	0.001	Not significant
LDL-C <2.5 mmol/l, *n* (%)	117 (47.4)	50 (24.4)	61 (37.0)	52 (26.4)	Not significant	0.001	0.082
Use of statins, *n* (%)	167 (65.0)	10 (4.7)	104 (62.3)	17 (8.4)	Not significant	0.001	Not significant
Fasting glycemia (mmol/l)	6.13 ± 1.69	6.11 ± 1.88	6.36 ± 1.16	5.64 ± 1.39	Not significant	0.005	0.009
Diabetes, *n* (%)	63 (26.5)	42 (19.8)	47 (31.8)	23 (11.4)	0.032	0.001	0.011
Use of oral antidiabetics or insulin	49 (19.1)	21 (9.9)	40 (24.0)	13 (6.4)	Not significant	0.001	Not significant (0.081)
Current smoking, *n* (%)	108 (42.0)	37 (17.5)	41 (24.6)	24 (11.9)	0.001	0.001	Not significant
eGFR (ml/min per 1.73 m^2)	76.1 ± 18.4	77.9 ± 12.3	69.5 ± 19.3	71.7 ± 13.1	0.001	Not significant (0.066)	Not significant
eGFR <60 ml/min per 1.73 m^2, *n* (%)	48 (18.8)	18 (8.5)	50 (30.1)	35 (17.3)	0.001	0.001	Not significant
Any antiplatelet drug	205 (79.8)	51 (24.1)	123 (73.7)	32 15.8)	0.038	0.001	Not significant
ASA alone, *n* (%)	145 (56.4)	45 (21.2)	85 (50.9)	32 (15.8)	Not significant	0.001	Not significant
ASA + dipyridamole, *n* (%)	7 (2.7)	0	7 (4.2)	0	Not applicable	Not applicable	
Clopidogrel, *n* (%)	50 (19.5)	4 (1.9)	28 (16.8)	0	Not significant (0.053)	0.001	0.034
Anticoagulants, *n* (%)	40 (15.6)	10 (4.7)	29 (17.4)	7 (3.5)	Not significant	0.001	Not significant

Not applicable, statistical analysis not applicable because of small numbers. ASA, acetylsalicylic acid; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

Hypertension control

There were 388 stroke survivors meeting the definition of hypertension. Based on the mean of the second and third measurements taken during the follow-up examination, they were divided into two subgroups and labeled as controlled (BP <140/90 mmHg) or uncontrolled (BP ≥140/90 mmHg) hypertensive patients (Table 3). These two groups differed only in the total number of antihypertensive drugs, higher in individuals with controlled BP (2.46 ± 1.25 vs. 1.95 ± 1.42; $P < 0.001$). Use of angiotensin-converting enzyme (ACE) inhibitors regardless of the number of antihypertensive drugs was associated with controlled hypertension. This was also the case of other antihypertensive drugs (mostly centrally acting drugs or alpha-blockers).

Using stepwise logistic regression, we found that the independent significant predictors of controlled hypertension include use of ACE inhibitors (odds ratio [OR] = 2.27), number of antihypertensive drugs (OR = 1.29 for each added drug), female gender (OR = 1.81), BMI less than 30 kg/m^2 (OR = 1.68), and university education (OR = 2.37). Age and depression score (Hospital Anxiety and Depression Scale) were not significant (Table 4). Thus, use of ACE inhibitors, higher number of antihypertensive drugs, female gender, BMI less than 30 kg/m^2, and university education contribute to better hypertension control.

Control of hypertension, defined as the proportion of individuals achieving BP lower than 140/90 mmHg, was significantly higher in cardioembolic stroke survivors as compared with those experiencing undetermined type of stroke (Fig. 1). For the purpose of this analysis, the group of cryptogenic strokes and that with incomplete examination were combined and labeled as 'undetermined'. On the contrary, other strokes and those of concomitant cause were excluded from this analysis because of small numbers.

DISCUSSION

Hypertension control

Hypertension is the most prevalent cardiovascular disorder substantially increasing the risk of cardiovascular disease, and stroke in particular. The relationship between BP and stroke is well documented for primary prevention [16]. However, the optimal BP for patients after stroke or transient ischemic attack has not been defined yet [17]. We found, in our group of mostly elderly patients surviving an ischemic stroke, a very frequent history of hypertension (73%) in the medical records during their hospitalization for acute stroke. At follow-up visit organized at a median of 16.5 months after the event, hypertension was detected in 93.7 and 88.0% of male and female stroke survivors, respectively. The 2013 ESH-European Society of Cardiology guidelines [18] recommend an SBP goal lower than

TABLE 3. Comparison of stroke survivors with controlled and uncontrolled hypertension

	BP <140/90 mmHg (controlled)	BP ≥140/90 mmHg (uncontrolled)	P
Number	166	222	
Age (years	68.1 ± 8.9	68.1 ± 9.2	Not significant
Men/women, *n* (%)	95/71 (57.2/42.8)	146/76 (65.8/34.2)	Not significant (0.086)
Concomitant cardiovascular disease, *n* (%)	32 (19.3)	48 (21.6)	Not significant
BP at discharge (mmHg			
SBP (mmHg)	142.8 ± 23.2	144.0 ± 21.9	Not significant
DBP (mmHg)	82.1 ± 13.1	82.4 ± 13.2	Not significant
Mean BP (mmHg)	102.3 ± 15.3	102.9 ± 14.8	Not significant
BMI (kg/m^2)	29.4 ± 5.25	29.9 ± 4.80	Not significant
BMI ≥30 kg/m^2 (%)	63 (38.0)	105 (47.3)	Not significant (0.070)
Current smoking, *n* (%)	56 (33.7)	76 (34.2)	Not significant
Diabetes, *n* (%)	39 (25.0)	53 (26.9)	Not significant
Modified Rankin Score	1 (0–2)	1 (0–2)	Not significant
MoCA	23 ± 5.6	24 ± 4.6	Not significant
Antihypertensive drugs			
Total number of antihypertensive drugs	2.46 ± 1.25	1.95 ± 1.42	0.001
Use of beta-blockers, *n* (%)	76 (45.8)	86 (38.7)	Not significant
Use of ACE inhibitors, *n* (%)	121 (72.9)	113 (50.9)	0.001
Use of ARBs, *n* (%)	27 (16.3)	48 (21.6)	Not significant
Use of calcium antagonists, *n* (%)	76 (45.8)	81 (36.5)	Not significant (0.065)
Use of diuretics, *n* (%)	65 (39.2)	69 (31.1)	Not significant (0.098)
Use of other antihypertensive drugs, *n* (%)	43 (25.9)	36 (16.2)	0.019

Data are presented as mean ± SD; median (interquartile range) or frequency (percentage). ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BP, blood pressure; MoCA, Montreal Cognitive Assessment; NIHSS, National Institutes of Health Stroke Scale.

140 mmHg to be considered in patients with previous stroke or transient ischemic attack. There is currently no evidence available that recurrent stroke could be prevented by initiating antihypertensive medication in the high-normal range, nor is there evidence for achieving SBP lower than 130 mmHg as suggested by previous guidelines [19]. The BP goal of lower than 140/90 mmHg was achieved in 39.8 and 48.3% of male and female poststroke patients with hypertension, respectively. Similar results were obtained in our population control group of about the same age. This may be just another example of physicians' inertia clearly showing lack of a differentiated approach to patients based on their total cardiovascular risk [20]. We must also admit that the evidence in favor of reducing SBP to lower than 140 mmHg does not apply to elderly hypertensive patients as all randomized clinical trials in the elderly have aimed at an SBP target lower than 150 mmHg and the achieved values have been more than 140 mmHg. Therefore, there is a need to test this question in a properly designed clinical trial, which is currently ongoing and endorsed by the EHS and the Chinese Hypertension League [21].

A stepwise logistic regression model showed that control of hypertension in our poststroke patients was associated with use of ACE inhibitors, number of antihypertensive drugs, female gender, BMI less than 30 kg/m^2, and university education. Mancia *et al.* [22], analyzing discontinuation of antihypertensive drug therapy in almost half a million new users of antihypertensive drugs in Lombardy, Italy, also found age-adjusted risk of discontinuation of antihypertensive treatment was lowest with angiotensin receptor blockers (ARBs) and ACE inhibitors. In our group of stroke survivors, ACE inhibitors were the most frequently used class of antihypertensive drugs, mostly in combination as monotherapy was not common. This is fully in line with the current ESH/European Society of Cardiology guidelines suggesting use of all drug regimens in patients with cerebrovascular disease provided that BP is effectively reduced [18]. In a smaller study using electronic pill boxes

TABLE 4. Logistic regression model of blood pressure control of stroke survivors at follow-up visit

	OR	95% CI	P
Age (1-year increase)	0.99	0.97–1.02	0.549
Sex (woman vs. man)	1.81	1.13–2.90	0.015
BMI (<30 kg/m^2 vs. ≥30 kg/m^2)	1.68	1.06–2.65	0.028
Education (university vs. other)	2.37	1.21–4.62	0.013
Number of antihypertensive drugs (increase by 1 drug)	1.29	1.09–1.53	0.004
Use of ACE inhibitors (yes vs. no)	2.27	1.42–3.65	0.001
HADS (score increase by 1 point)	0.99	0.94–1.04	0.620

ACE, angiotensin-converting enzyme; CI, confidence interval; HADS, Hospital Anxiety and Depression Scale; OR, odds ratio.

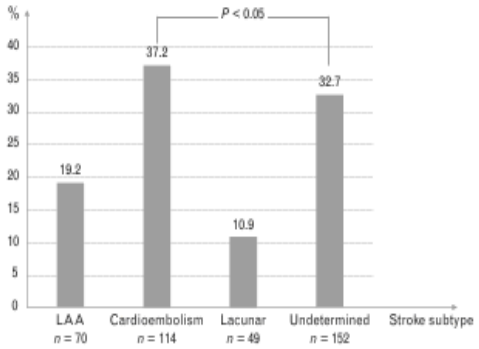

FIGURE 1 Control of hypertension (BP <140/90 mmHg) by stroke subtype in survivors. LAA, large artery atherosclerosis.

to assess treatment compliance, female gender was associated with a better outcome in terms of compliance [23].

In the Perindopril Protection Against Recurrent Stroke Study trial, there was overall no mean difference in BP by BMI quartiles [24]. The current hypertension guidelines [18] do not specifically address the issue of obesity and hypertension. Moreover, there are no large clinical trials focusing on hypertension and obesity. The European Society of Hypertension Working Group on Obesity proposes ACE inhibitors as the most appropriate drug for the treatment of hypertension in obese patients [25].

There are only a few studies analyzing BP control in poststroke patients. In the North East Melbourne Stroke Incidence Study [26], BP data 5 years poststroke (first ever) were obtained in 325 patients. Hypertension was found in 82%, with BP lower than 140/90 mmHg in 52%. In France, a total of 570 patients with a history of stroke were identified within ECLATI, a cross-sectional study conducted by French general practitioners in 2000. In this sample, hypertension control was achieved in a lower percentage of patients than those with myocardial infarction (24.6 vs. 34.2%) [27]. A total of 495 stroke survivors were identified within the National Health and Nutrition Examination Survey from 1999 to 2004 [8]. Hypertension was found in 71.7%, with BP lower than 140/90 mmHg achieved by 46.5%, that is, results very similar to ours. In the so far largest clinical trial of poststroke patients, less than a third of patients with stroke had BP controlled at least 75% of the time for 2 years [28].

Obesity and diabetes

No association between obesity and risk of recurrent stroke has been established [29,30]. Paradoxically, poststroke mortality and morbidity may be lower in overweight stroke survivors as compared with normal weight ones [31].

In poststroke patients, sarcopenic obesity may contribute to the high prevalence of impaired glucose tolerance and diabetes mellitus [32]. We found, in our poststroke patients, a significantly higher prevalence of diabetes only in women as compared with controls (31.8 vs. 11.4%; $P < 0.001$). This gender difference may reflect the higher cardiovascular risk of diabetes in women [33,34]. Reduced physical activity and disability in poststroke patients predispose to weight gain, insulin resistance, and diabetes mellitus. The mechanism also includes loss of skeletal muscle. Hemiparetic muscle may undergo intramuscular fat accumulation and a switch from slow-twitch fibers to fat myosin heavy chains [35,36].

Dyslipidemia and lipid-lowering drugs

Unlike the undoubtable relationship between total cholesterol and risk of fatal myocardial infarction, the relationship between total cholesterol and risk of stroke remains to be controversial [37] as earlier studies did not differentiate between ischemic and hemorrhagic stroke. On the contrary, large clinical randomized trials with statins in patients with CHD or at high cardiovascular risk found a decrease in stroke incidence [38]. Most of the current guidelines [39,40,18] agree that patients with ischemic stroke should be treated with statins although direct evidence for this recommendation is still lacking.

The Stroke Prevention by Aggressive Reduction in Cholesterol Levels trial, so far the only large clinical trial in poststroke patients, showed that lowering LDL-cholesterol to 1.9 mmol/l rather than having 3.3 mmol/l on placebo can reduce recurrent stroke by about 16% [41]. The study design did not distinguish between ischemic and hemorrhagic stroke as the qualifying event for enrolment into the study. Although no clinical trial has to date compared more or less aggressive LDL-cholesterol lowering therapy in patients surviving an ischemic stroke [17], the recommended target LDL is < 2.5 mmol/l or, possibly, < 1.8 mmol/l.

We found, in our study, significantly lower total and LDL-cholesterol in stroke survivors of both sexes than in controls. However, the proportion of poststroke patients achieving LDL-cholesterol lower than 2.5 mmol/l was only 47.4% in men and 37.0% in women despite the fact statins were frequently prescribed (65% in men, 62.3% in women).

Other secondary prevention measures

The high prevalence of smoking at the follow-up visit (42% in men and 24.6% in women) documents the poor adherence to lifestyle measures and low implementation of guideline recommendations.

Antiplatelet drugs are considered an integral part of secondary prevention in patients surviving an ischemic stroke unless there is a contraindication or they require anticoagulation therapy (most likely because of atrial fibrillation). The European Guidelines [39,42] recommend a combination of low-dose ASA and dipyridamole, or clopidogrel alone as therapy of first choice in patients with noncardioembolic ischemic stroke. In our poststroke patients, the majority of antiplatelet drugs were represented by low-dose ASA followed by clopidogrel, whereas the combination of ASA and dipyridamole was only taken by 3.3% of our patients.

A relatively high proportion of the poststroke patients reported use of antiplatelet drugs (79.8% of men and 73.7% of women). We have to admit the use of drugs in general was not verified by any objective measure.

Study limitations and strengths

Our group of 424 poststroke survivors was derived from 736 consecutive patients hospitalized for their first-ever ischemic stroke in two major healthcare centers in the Czech Republic. They were compared with controls of similar age and from the same geographic region. The response rates of stroke patients and the general population were also very similar (69.7 and 62.6%, respectively). Laboratory analyses were performed for both the study and control populations at the same laboratory with certified accuracy.

Thus, our stroke population is very close to a hospital-based registry and we do not have information about stroke patients not admitted to hospital or dying before admission. Another study limitation is that the follow-up examination was performed 6–36 months since the acute event and no follow-up information is available about those who died either during hospitalization or prior to follow-up visit.

The size of our population of 424 stroke survivors may not be impressive; however, it is fully comparable with the

other published studies [8,27,28] and, as a matter of fact, the study is the first of its kind presenting data from Central Europe.

In conclusion, we found a high prevalence of major cardiovascular risk factors in patients surviving their first-ever ischemic stroke, with hypertension being the most prevalent one and affecting more than 90% of the study population. Despite the fact that 80% of the hypertensive patients report taking antihypertensive medication, a BP lower than 140/90 mmHg is achieved by less than 40%. Similarly, statins are taken by 60% of poststroke patients, but LDL-cholesterol lower than 2.5 mmol/l is achieved by less than 50%. Our results indicate failure of lifestyle measures as one third of poststroke patients continue smoking and obesity affects about 40% of poststroke survivors. Data on use of antiplatelets and anticoagulants are relatively satisfactory. Overall, our findings are consistent with poor implementation of guidelines for secondary prevention in clinical practice. As most of poststroke patients are treated by general practitioners, our results highlight the need for specifically addressing the general practitioners to recall the importance of hypertension control and other secondary preventive measures.

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Conflicts of interest

There are no conflicts of interest.

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ORIGINAL ARTICLE

Quality of Life Predictors in Chronic Stable Post-Stroke Patients and Prognostic Value of SF-36 Score as a Mortality Surrogate

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Abstract Perceived quality of life (QoL) and psychological well-being represents an important target of secondary prevention practice in post-stroke patients. We aimed to identify the major covariates of impaired QoL in stable post-stroke patients and whether impaired QoL itself represents independent mortality predictor.

The study consisted of a cross-sectional and a prospective part. Three hundred forty-one patients [mean age 69.0 (SD 9.1)] were interviewed at least 6 months after discharge from hospital for their first-ever ischemic stroke. QoL was objectivized using 36-Item Short-Form Health Survey (SF-36) scoring. Standard health-related questionnaires, including Hospital Anxiety and Depression Scale (HADS), risk factors, and biochemical markers, were assessed. To estimate the 5-year all-cause and cardiovascular mortality, we ascertained the vital status and declared cause of death.

Anxiety, depression (HADS score ≥11), brain natriuretic peptide levels ≥100 ng/mL, residual motor impairment at interview, Rankin Scale ≥4 at discharge from hospitalization, and raised blood pressure were identified as main determinants of impaired QoL in the cross-sectional part. The 5-year all-cause and cardiovascular mortality rates were 25.8 and 19.9 %, respectively. After adjustment for potential covariates, patients with an SF-36 score ≤40 at baseline had more than a twofold higher risk of all-cause and cardiovascular mortality (with HRRs 2.01 (95 % CI 1.21–3.32), $p<0.007$ and 2.32 (95 % CI 1.32–4.09), $p<0.003$, respectively) during the 5 years of follow-up.

In conclusion, anxiety, depression, and raised brain natriuretic peptide levels were the most important covariates of impaired QoL in post-stroke patients. Moreover, a decreased SF-36 score (≤40) represents an independent surrogate of increased additive mortality risk.

Keywords Ischemic stroke · Quality of life, anxiety · Depression · SF-36 score · Mortality

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Introduction

Stroke represents one of the most important factors of global burden of cardiovascular disease in the general population and is a leading cause of chronic disability in elderly and middle-aged adults [1]. Principles of stroke care organization, management in the acute phase, rehabilitation, and prevention in Europe were extensively defined by a consensus conference in Helsingborg in 2006 (known as the Helsingborg Declaration) [2]; several other guidelines [3] were published afterwards, with the most recent one in 2014 [4] Cerebrovascular disease is a heterogeneous clinical syndrome consisting of different pathophysiological and aetiological subgroups, but ischemic stroke is the most frequent subtype. Secondary prevention principles in ischemic stroke patients are nearly similar to

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coronary heart disease. Therefore, since the Third Joint ESC Guidelines [5], effective prevention in patients with established cerebrovascular disease has also been defined as a priority in clinical practice.

On the other hand, stroke often impairs a patient's life to a greater extent than coronary heart disease. Patients can lose their self-care ability or social role, are unable to handle daily activities, and develop depression and anxiety [6, 7]. Despite the indisputable therapeutic advances in post-stroke management in the acute phase, implementation of secondary prevention principles in clinical practice is far from being optimal [8] and objective epidemiological data about factors of psychosocial well-being are more-than-less anecdotal.

In the present study, we sought to identify, in a cross-sectional survey, the major clinical and psychosocial covariates of perceived quality of life (QoL) in chronic stable patients after their first-ever ischemic stroke. Moreover, in the second part of the present analysis, we aimed to determine, in a prospective mortality cohort study, whether impaired QoL itself, objectivized using a decreased 36-Item Short-Form Health Survey Quality of Life (SF-36) score at baseline can be used as a global surrogate indicator of future increased mortality risk.

Materials and Methods

Study Population and Study Design

The study population consists of Czech patients examined within the framework of a well-defined survey in patients after their first-ever ischemic stroke (Eurospire III—stroke-specific module) in 2007. Selection of patients and the study protocol have been described in detail elsewhere [8]. This survey was conducted in two centers in the Czech Republic: University Hospital Pilsen and the Cardio Center of the Institute for Clinical and Experimental Medicine in Prague.

Patients with the diagnosis of ischemic stroke were identified from hospital discharge lists. Stroke was defined according to the World Health Organization criteria [9], and the ischemic aetiology of stroke was verified by brain imaging. Patients with recurrent stroke events (a previous transient ischemic attack was acceptable), secondary intracranial bleeding, aged more than 80 years at the time of the index event, patients not living in the study region, and those who had deceased during the index (stroke) hospitalization were excluded. The recruitment was done retroconsecutively (i.e., starting with the most recent stroke patient backward until the planned pool of ~500 patients was reached). Finally, a total of 507 patients met the inclusion criterion (i.e., first verified ischemic stroke), but of this number, 77 died after discharge from the index hospitalization, i.e., 430 patients were finally invited, and the overall respondence rate to a baseline interview was 79.3 % of the initially identified stroke patients.

The present study consists of two parts: a retrospective cross-sectional survey (to identify the predictors of impaired QoL) and a prospective cohort study (to establish the risk of impaired QoL in terms of all-cause or cardiovascular fatal outcomes).

Clinical Examinations

The interview was performed at least 6 months after admission for the index stroke event, during a single (lasting about 3 months) campaign. Information on the personal and demographic characteristics, personal and family history of coronary heart disease, lifestyle, and pharmacotherapy were obtained. The following clinical examinations were performed: Height and weight were measured in light indoor clothes without shoes using SECA 220 scales and measuring sticks. Waist circumference was measured using a steel tape measure. Blood pressure (BP) was measured twice in the sitting position on the right arm using a standard mercury sphygmomanometer (and the average value was used). A standard 12-channel ECG was obtained in all patients, and the presence of atrial fibrillation was considered by the examiner. Breath carbon monoxide was measured by a SMOKERLYSER device (model EC 50, Bedfont Scientific, Upchurch, UK) to verify the reported smoking habit. A current (i.e., at time of interview) distinct neurological deficit (aphasia, dysphasia, facial palsy, limb paresis, or several sensitive deficits) was assessed by the examiner (a physician specialized in internal medicine), while disability at discharge from the index event was considered using information in the discharge summary and/or neurological examination in the hospital records and subsequently quantified on the modified Rankin Scale (mRS) [10]. Barthel Activities of Daily Living (ADL) Index questionnaire was completed by the examiner at interview, based on patient's recent functional status [11].

Biochemical Examination

Venous blood samples were drawn after at least 12 h of overnight fasting. All laboratory examinations were performed in series from aliquots stored at −70 °C and included estimation of serum total (TCHOL) and HDL (HDL) cholesterol using an ARCHITECT c800 analyzer (Abbott Laboratories, Wiesbaden, Germany) and DOT Diagnostics commercial kits (Prague, Czech Republic); the same analyzer was used for measuring serum triglycerides (TG) and glucose (GLU), whereas brain natriuretic peptide (BNP) was measured in EDTA plasma using Abbott commercial kits. HbA1c was estimated by ionex liquid chromatography using a G7 analyzer (TOSOH, Shunan, Japan). LDL was calculated by the

Friedewald equation, i.e., LDL=TCHOL−HDL−(TG/2.22) when TGs≤4.5 mmol/L.

Quality of Life and Psychological Well-Being Assessment

The following standard health-related self-reported questionnaires were completed by subjects: Hospital Anxiety and Depression Scale (HADS) [12] and the 36-Item Short-Form Health Survey Quality of Life (SF-36) to quantify QoL [13]; we used validated available Czech localizations of these questionnaires.

The Hospital Anxiety and Depression Scale is a commonly used questionnaire assessing psychiatric and mood disorders by relying on the feelings from the previous week. It contains 14 questions: 7 questions on depression and 7 on an anxiety subscale. Each question has four dimensions rated from 0 (no symptoms) to 4 (maximum impairment). In the present study, we set a threshold of ≥11 as an index for highly suspected psychological/mood distress (and categorized as "anxiety symptoms" and "depression symptoms" presence) [12].

The SF-36 questionnaire investigates the following perceived social and physical QoL domains: physical functioning, role limitation because of physical problems, bodily pain, general health, vitality, social functioning, role limitation because of emotional problems, and mental health. Moreover, three summary items were calculated: a physical component summary, a mental component summary, and total SF-36 score. The scoring manual [13] was employed to generate scores (0–100) for each domain including the summary items.

Data Analysis

Data obtained at interview were used for the cross-sectional part of the study and as baseline data for the prospective part. Moreover, for prospective mortality analysis, we ascertained the vital status of patients through May 31, 2012 using the National Mortality Registry of the Czech Institute for Medical Information and Statistics. The mortality (censoring) data are available for all patients. We used the International Classification of Diseases, Revision 10 (ICD-10) codes in death certificates and available medical documentation from hospital or outpatient clinic to adjudicate the cause of death (each fatal case was adjudicated by two separate investigators). Power calculations revealed that our population of patients was sufficiently large to estimate the expected 5-year mortality rate with a 5 % relative precision level.

The total SF-36 score was employed not only as continuous variable but, for the purpose of regression models (logistic regression and Cox proportional hazard model), also dichotomized using an arbitrary ≤40 cutoff value (upper limit of the bottom quintile) as "impaired QoL." A modified Rankin Scale higher than 3 was considered as "poor functional status at discharge." Barthel ADL Index was categorized as independent (100 points), mild dependency (65–95 points), and moderate dependency (45–60 points)—no subject was severely dependent [11].

Presence of facial palsy or limb paresis at interview was considered as "residual motoric impairment," while presence of aphasia or dysartia as "residual speech impairment." A patient was labeled as a "current smoker" if he/she self-reported it or had a carbon monoxide in breath value exceeding 10 ppm at the time of interview. Conventional risk factors were dichotomized by usual target values according to the current guidelines [5] (see relevant section of tables). As elevated BNP were considered concentration above 100 ng/mL [14]. For statistical analyses, we used STATISTICA 8 and STATA/SE 8 software. Standard statistical methods were used, i.e., the Mann–Whitney *U*, multiple stepwise logistic regression, and Cox proportional hazard regression.

Results

Characteristics of Participants

A total of 341 patients with a mean age of 69.0 (±SD 9.1) years were interviewed at least 6 months after first-ever stroke manifestation [median time (interquartile range) between stroke and interview was 19 (11.3–28.7) months] and then followed in the prospective study. The baseline characteristics at interview are given in Table 1.

Descriptive statistics of QoL and psychological well-being assessment are shown in Table 2. Of single QoL dimensions (ascertained by the SF-36 questionnaire) "role limitation because of physical problems," "general health," and "vitality" seem to be the major components of impaired global QoL (quantified using the SF-36 score). Summarized physical and mental dimensions contributed to perceived QoL (total SF-36 score) nearly equally.

Quality-of-Life Determinants

Table 3 shows the total SF-36 score compared according to the presence or absence of a large set of patient characteristics. A significantly lower SF-36 score (i.e., generally poorer QoL) was found in patients older than 64 years, those with increased BNP, residual motoric impairment, residual speech impairment, poor functional status at discharge from stroke hospitalization, and in patients with symptoms of anxiety or depression (compared to subjects without these single characteristics). Moreover, males showed higher SF-36 scores than females.

Using multiple linear stepwise regression, SF-36 score as continuous variable independently inversely correlate with age, BNP, HADS score for anxiety and depression, and with modified Rankin score at discharge from hospitalization

Table 1 Baseline characteristics of study sample [mean (standard deviation) or proportion]

n	341
Median time (interquart. range) to interview[a] [years]	1.64 (1.00–2.44)
Age [years]	69.0 (9.1)
Male gender [%]	58.9
Current smoking [%]	15.8
Body mass index [kg/m^2]	29.1 (5.0)
Waist circumference [cm]	100.2 (12.8)
Systolic BP [mmHg]	137.5 (19.3)
Diastolic BP [mmHg]	80.1 (10.4)
Treatment with antihypertensives	88.3
Treatment with ACEIs or ARBs [%]	68.9
Brain natriuretic peptide [ng/L]	71.1 (118.5)
Atrial fibrillation[b] [%]	19.1
Treatment with warfarin [%]	17.6
Total cholesterol [mmol/L]	5.11 (1.11)
HDL cholesterol [mmol/L]	1.39 (0.39)
LDL cholesterol [mmol/L]	3.08 (0.96)
Triglycerides [mmol/L]	1.58 (0.80)
Treatment with statins [%]	52.2
Fasting glycemia [mmol/L]	6.81 (2.60)
Hemoglobin A1c [mmol/mol]	45.1 (12.1)
Treatment with antidiabetics [%]	22.3
Residual motoric deficit[b] [%]	25.0
Residual speech impairment[b] [%]	5.6
Modified Rankin score[c]	1.9 (1.23)
Barthel ADL Index[b]:	
>95	86.2
65–95	11.7
<65	2.1

BP blood pressure, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *ACEi* angiotensin-converting enzyme inhibitor, *ARB* angiotensin II receptor blocker, *HADS* Hospital Anxiety Depression Scale, *SF-36* 36-Item Short-Form Health Survey Quality of Life, *ADL* activities of daily living

[a] Time between admission for stroke and interview

[b] At the time of interview

[c] At discharge from stroke hospitalization

Table 2 Descriptive data of quality of life and psychological well-being assessment by SF-36 and HADS questionnaires

	Mean (standard deviation)	Median (interquartile range)
SF-36 questionnaire scores:		
Physical functioning	64.7 (28.0)	70 (45–90)
Role limitation by physical problems	51.9 (40.6)	50 (0–100)
Bodily pain	72.6 (27.6)	74 (51–100)
General health	50.7 (21.1)	50 (35–67)
Vitality	58.5 (21.6)	60 (45–75)
Social functioning	74.0 (25.9)	75 (62.5–100)
Role limitation by emotional problems	57.1 (40.0)	66.7 (33.3–100)
Mental health	71.4 (19.6)	76 (60–88)
Physical component summary score	59.7 (22.3)	59.3 (41.4–79.8)
Mental component summary score	62.3 (20.7)	64 (46.8–79.8)
Total SF-36 score	62.6 (21.6)	62.1 (45.3–81.5)
Hospital Anxiety and Depression Score:		
Anxiety score	4.7 (3.7)	4 (2–7)
Depression score	5.9 (4.0)	6 (2–9)

(Table 4, model A). In addition, SF-36 score was inversely associated with residual motoric impairment as categorized independent variable.

In stepwise multiple logistic regression analysis (Table 4, model B), we identified the following covariates as significant positive independent determinants of impaired QoL (dichotomized as a SF-36 score ≤40): raised blood pressure, BNP ≥100 ng/mL, residual motoric impairment at interview, and poor functional status at discharge. The highest predictive power was found for anxiety and depression symptoms (defined as a corresponding HADS score ≥11). However, similar results were obtained when anxiety or depression were dichotomized by HADS score ≥8, with the respective odd ratios (95 % CI) for anxiety and depression of 4.64 (2.13–10.13) and 10.99 (4.91–24.57)—*not in table section.*

Mortality Follow-Up Analysis

During a median follow-up of 1959 days (5.4 years), 97 patients deceased (28.5 %) with 75 of these fatal events considered cardiovascular. Of this number, only nine patients died from recurrent ischemic stroke, while two from intracerebral hemorrhage. The corresponding 5-year all-cause and cardiovascular mortality rates were 25.8 and 19.9 %, respectively. Figure 1 shows the Kaplan–Meier survival curves. Impaired QoL (total SF-36 score ≤40) was associated with significantly decreased survival.

We further analyzed the all-cause 5-year mortality predictors using a multivariable adjusted Cox model (Table 5). Model A includes conventional risk factors and treatments (as potential covariates) *plus* the categorized SF-36 score, with increased BNP (≥100 ng/mL) added only to model B. After adjustment for covariates, patients with SF-36 scores ≤40 had more than twofold higher risk of 5-year all-cause or cardiovascular mortality even if adjusted for increased BNP (as strongest

Table 3 Unifactorial association between QoL (total SF-36 score) and risk profile, treatments, and patient characteristics

Factor	Prevalence of factor [%]	Mean total SF score (±SD) for factor present	Mean total SF score (±SD) for factor absent	*p* Value
Age ≥65 years	70.0	60.9 (21.5)	66.2 (21.8)	0.036
Male gender	58.8	66.0 (21.2)	57.8 (21.2)	<0.001
Current smoking	16.0	61.7 (22.8)	62.9 (21.4)	0.837
Body mass index ≥30 kg/m[b]	38.8	63.3 (21.2)	62.3 (21.8)	0.705
Increased waist circumference[a]	61.0	61.2 (21.3)	65.2 (21.8)	0.093
Raised blood pressure[b]	46.2	64.2 (22.0)	61.2 (21.2)	0.229
LDL cholesterol ≥2.5 mmol/L	67.6	62.7 (21.2)	62.2 (22.4)	0.872
Inadequate glycemic control[c]	33.7	63.7 (20.6)	62.5 (21.9)	0.613
Treatment with ACEIs or ARBs	68.9	62.7 (20.9)	62.5 (22.9)	0.997
Treatment with statins	52.2	63.3 (20.8)	61.9 (22.3)	0.631
Brain natriuretic peptide >100 ng/mL	19.1	55.3 (21.5)	64.4 (21.2)	0.005
Atrial fibrillation	19.1	56.0 (21.2)	63.3 (21.3)	0.086
Residual motoric impairment	25.0	49.4 (19.1)	66.8 (20.6)	<0.001
Residual speech impairment	5.6	54.8 (21.5)	61.2 (21.5)	0.017
Poor functional status at discharge[d]	22.3	45.8 (20.8)	64.7±20.72	<0.001
Anxiety symptoms[e]	7.8	39.9 (15.8)	64.6±20.85	<0.001
Depression symptoms[e]	12.3	40.6 (20.1)	65.8±19.84	<0.001

p Value by Mann–Whitney *U* test

[a] ≥102 cm in males and ≥88 cm in females

[b] Systolic BP ≥140 and/or diastolic BP ≥90 mmHg

[c] Fasting glucose ≥7 mmol/L and/or HbA1c ≥48 mmol/mol

[d] Modified Rankin score at discharge from index (stroke) hospitalization ≥4

[e] HADS score for anxiety or depression ≥11

mortality predictor) in model B. Model B was performed also with physical component summary score of SF-36 questionnaire with nearly similar results [all-cause and cardiovascular mortality HRRs for physical component summary score ≤40 were 1.79 (95 % CI 1.10–2.94) and 1.98 (95 % CI 1.13–3.45), respectively—*not in table section*], while mental component summary score predicted significantly only all-cause mortality [all-cause and cardiovascular mortality HRRs for mental component summary score ≤40 were 1.77 (95 % CI 1.02–3.06) and 1.67 (95 % CI 0.89–3.15), respectively—*not in table section*].

Table 6 shows predictive power of other major covariates of QoL (in regression model, similar model B of Table 5) on all-cause and cardiovascular mortality. Only residual motoric impairment independently increased all-cause mortality risk if adjusted for SF-36 ≤40 and other confounders. Moreover, SF-36 ≤40 maintained its predictive power even if all four additional major covariates of QoL (i.e., residual motoric impairment, poor functional status at discharge, and HADS score for anxiety or depression ≥11) were included into one regression model [all-cause and cardiovascular mortality HRRs for SF-36 score ≤40 were 2.03 (95 % CI 1.11–3.71) and 2.31 (95 % CI 1.19–4.50), respectively—*not in table section*].

Discussion

The key finding in our study is that impaired QoL categorized as a decreased SF-36 score (≤40) may serve as a mortality surrogate independent of the conventional risk profile in stable patients after their first-ever (predominantly mild to moderate) ischemic stroke. Therefore, a decreased SF-36 score may potentially serve as a simple indicator of additive mortality risk in secondary prevention. Although the SF-36 score is derived from only subjective and non-specific symptoms, it may help to improve the risk stratification in secondary prevention of vascular disease parallel to conventional tools (disease-specific symptoms, control of risk factors, etc.). To our knowledge, this is the first study using the SF-36 score as an independent prognostic factor in the setting of chronic cardiovascular patients, but equivalent results were reported in patients admitted to intensive care units. A recent prospective study by Bukan and colleagues [15] found, in 318 patients admitted to an intensive care unit, that pre-admission QoL, assessed by the SF-36, acts as a significant independent predictor of in-hospital, 30-, and 90-day mortality. Similar results in the same settings were reported by Hofhuis et al. [16] and Welsh et al. [17]. We also tested the fitness of other quantitative determinants of QoL (such as motoric deficit, initially poor functional

Table 4 Adjusted multivariate association between QoL (total SF-36 score) as a dependent variable and risk profile, treatments, and patient characteristics as its covariates

Model A (continuous)[a]:		
Age	−0.230 (0.095)	0.016
Brain natriuretic peptide	−0.026 (0.008)	0.002
Residual motoric impairment	−6.405 (2.242)	0.005
Modified Rankin score at discharge	−2.741 (0.765)	<0.0001
HADS score for anxiety symptoms	−2.297 (0.250)	<0.0001
HADS score for depression symptoms	−1.829 (0.250)	<0.0001
const.	109.35 (6.586)	<0.0001
Model B (categorized)[b]:		
Raised blood pressure	2.46 (1.10–5.49)	0.028
Treatment with ACEis or ARBs	0.47 (0.21–1.05)	0.065
Brain natriuretic peptide >100 ng/mL	2.89 (1.22–6.82)	0.016
Residual motoric impairment	3.58 (1.57–8.16)	0.002
Poor functional status at discharge	3.29 (1.26–8.58)	0.015
HADS score for anxiety symptoms ≥11	17.35 (5.02–59.90)	<0.0001
HADS score for depression symptoms ≥11	11.82 (4.71–29.65)	<0.0001

[a] Multiple stepwise linear regression, total SF-36 as dependent continuous variable, beta coefficients (standard error of beta), and *p* values are depicted; the following variables were initially included in the full model in addition: age, male gender, current smoking, body mass index, waist circumference, mean arterial pressure, LDL, hemoglobin A1c, treatment with ACEis or ARBs, treatment with statins, treatment with antidiabetics, treatment with warfarin, atrial fibrillation, and residual speech impairment

[b] Multiple stepwise logistic regression, total SF-36 score ≤40 as dependent variable, odds ratio (95 % confidence intervals), and *p* values are depicted; the following variables were initially included in the full model in addition: age ≥65 years, male gender, current smoking, body mass index ≥30 kg/m^2, increased waist circumference, treatment with any antihypertesives, LDL ≥2.5 mmol/L, treatment with statins, inadequate glycemic control, treatment with antidiabetics, treatment with warfarin, atrial fibrillation, and residual speech impairment

outcomes of stroke, and presence of symptoms of anxiety or depression), but these variables did not substantially improved the additive mortality prediction over SF-36 score.

In contrast, therapeutic control of conventional risk factors (with the exception of glucose metabolism) generally did not influence mortality risk. In our sample, the best predictive power in terms of all-cause and cardiovascular mortality prediction was associated with elevated BNP concentration. Patients with BNP >100 ng/mL showed about fourfold higher risk of all-cause or cardiovascular-related death. Indeed, the majority of those with elevated BNP were not recognized as heart failure patients (only less than 3 % were treated with loop diuretics, had known left ventricular dysfunction, or report symptoms of heart failure greater than NYHA I), i.e., most of the elevated BNP cases were subclinical. Natriuretic peptides (BNP or N-terminal-proBNP) are not only well clinically established biomarkers of heart failure but, also, powerful predictors of cardiovascular mortality and morbidity. The prognostic importance of natriuretic peptides is evident in various clinical settings, in patients with severe [18] or stable chronic [19] heart failure, acute coronary syndrome [20], or stable coronary heart disease [21] as well as in the general population [22]. The predictive potential of natriuretic peptides is also evident in the setting of stroke patients. A recent study by Nigro and colleagues [23] reported that in a sample of 441 patients, elevated BNP independently predicted all-cause mortality as early as 90 days post-stroke and, also, after 1 year of follow-up. BNP also predicts in-hospital mortality in acute stroke [24], functional outcomes at 3 or 6 months post-stroke (using the modified Rankin Scale) [25, 26]. However, all these results are based on acute concentrations, because, in these studies, BNP was generally collected upon admission. In the present study, we found that increased BNP concentration maintains its prognostic importance also in rather stable post-stroke patients, i.e., when collected 6–36 months post-stroke (median, 1.6 years).

To our knowledge, our study is also the first to report the independent association of mild elevation of BNP and QoL in the setting of stable post-stroke patients. Anticipated strong factors of QoL in post-stoke patients such as residual motoric impairment or an initially poor outcome of stroke (quantified by mRS at discharge) indicated impaired QoL (objectivized by the SF-36 score) in nearly similar extent as increased BNP.

In our sample, psychosocial factors were identified as the most powerful covariates of QoL. In fact, the presence of anxiety symptoms increased the risk of impaired QoL more than 15 times, while the presence of depression symptoms more than 12 times. It is well evident that post-stroke depression (PSD) represents a major medical problem in stroke patients. The prevalence of PSD was reported to be between 10

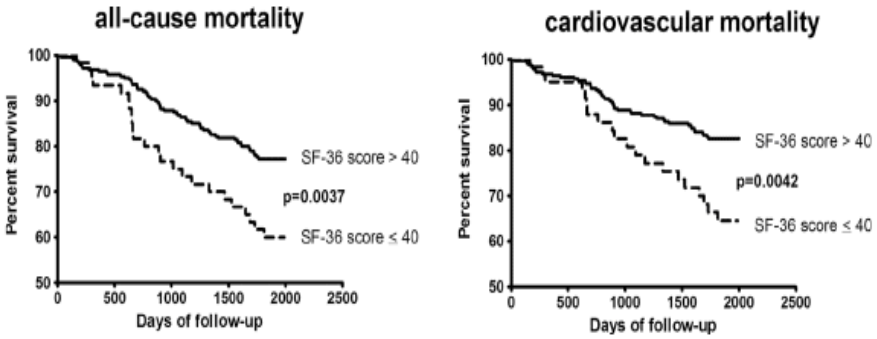

Fig. 1 Kaplan–Meier survival curves for all-cause and cardiovascular mortality by the SF-36 score (*p* value by the Mantel–Cox test)

and 65 % depending on the stroke phase [7]. Stroke was also identified as a significant risk factor for suicide, particularly in young adults and women [27]. PSD is more frequent in the acute phase of stroke with the risk peaking in the first 3–6 months and declining during the chronic phase [28]. In the present study, symptoms of depression were found in only 12.3 % of subjects as a result of the strict criterion as the cutoff (HADS score ≥11). When using less strict criteria ≥8, depression symptom prevalence rose in our sample up to 33.4 %, while the risk of impaired QoL decreased only marginally

Table 5 5-Year mortality predictors in models excluding or including BNP (Cox proportional hazard model)

	Model A (excluding BNP)		Model B (including BNP)	
	Hazard ratio (95 % CI)	*p* Value	Hazard ratio (95 % CI)	*p* Value
All-cause mortality:				
Age ≥65 years	3.27 (1.73–6.16)	<0.0001	2.79 (1.46–5.35)	0.002
Male gender	1.39 (0.83–2.23)	0.180	1.59 (0.97–2.59)	0.065
Current smoking	1.21 (0.64–2.89)	0.560	1.45 (0.76–2.77)	0.264
Body mass index ≥30 kg/m^2	0.73 (0.45–1.20)	0.211	0.82 (0.50–1.35)	0.439
Raised blood pressure	0.77 (0.48–1.21)	0.255	0.86 (0.54–1.39)	0.549
LDL ≥2.5 mmol/L	0.72 (0.43–1.20)	0.206	0.69 (0.41–1.16)	0.160
Inadequate glycemic control	1.92 (1.20–3.07)	0.006	1.80 (1.12–2.88)	0.015
Atrial fibrillation	2.14 (1.15–3.97)	0.016	1.81 (0.99–3.23)	0.055
Treatment with ACEi or ARBs	1.02 (0.62–1.66)	0.950	0.80 (0.49–1.33)	0.397
Treatment with statins	0.88 (0.54–1.43)	0.596	0.88 (0.53–1.42)	0.588
Treatment with warfarin	0.79 (0.35–1.78)	0.562	0.53 (0.24–1.20)	0.129
Brain natriuretic peptide >100 ng/mL	–	–	3.34 (1.98–5.65)	<0.0001
Total SF-36 score ≤40	2.31 (1.41–3.77)	0.001	2.01 (1.21–3.32)	0.007
Cardiovascular mortality:				
Age ≥65 years	2.76 (1.37–5.56)	0.004	2.29 (1.12–4.70)	0.024
Male gender	1.38 (0.80–2.39)	0.247	1.59 (0.90–2.81)	0.107
Current smoking	0.93 (0.43–2.01)	0.846	1.16 (0.53–2.54)	0.705
Body mass index ≥30 kg/m^2	0.56 (0.31–1.01)	0.053	0.72 (0.40–1.31)	0.159
Raised blood pressure	0.83 (0.49–1.40)	0.485	0.96 (0.55–1.66)	0.875
LDL ≥2.5 mmol/L	0.75 (0.42–1.35)	0.337	0.72 (0.40–1.26)	0.281
Inadequate glycemic control	1.92 (1.12–3.28)	0.017	1.78 (1.03–3.06)	0.037
Atrial fibrillation	2.57 (1.31–5.07)	0.006	2.08 (1.06–4.08)	0.033
Treatment with ACEi or ARBs	0.95 (0.54–2.65)	0.846	0.71 (0.40–1.26)	0.246
Treatment with statins	1.05 (0.51–1.84)	0.855	1.05 (0.59–1.85)	0.877
Treatment with warfarin	0.63 (0.25–1.63)	0.344	0.43 (0.17–1.11)	0.081
Brain natriuretic peptide >100 ng/mL	–	–	4.78 (2.55–8.93)	<0.0001
Total SF-36 score ≤40	2.73 (1.57–4.73)	<0.0001	2.32 (1.32–4.09)	0.003

Table 6 Fully adjusted predictive power of other major QoL covariates on 5-year mortality in models excluding or including SF-36 score (Cox proportional hazard model)

	Model A (excluding SF-36 score ≤40)		Model B (including SF-36 score ≤40)	
	Hazard ratio (95 % CI)	*p* Value	Hazard ratio (95 % CI)	*p* Value
All-cause mortality:				
Residual motoric impairment	2.56 (1.57–4.18)	<0.0001	1.90 (1.09–3.30)	0.021
Poor functional status at discharge	1.81 (0.95–3.46)	0.072	1.48 (0.73–3.01)	0.280
HADS score for anxiety ≥11	0.54 (0.19–1.52)	0.244	0.32 (0.11–1.03)	0.072
HADS score for depression ≥11	1.32 (0.72–2.42)	0.368	1.02 (0.52–2.00)	0.958
Cardiovascular mortality:				
Residual motoric impairment	2.65 (1.51–4.63)	0.004	1.88 (0.99–3.55)	0.051
Poor functional status at discharge	2.57 (1.28–5.17)	0.008	2.15 (0.99–4.65)	0.052
HADS score for anxiety ≥11	0.71 (0.25–2.05)	0.533	0.42 (0.13–1.31)	0.133
HADS score for depression ≥11	1.34 (0.68–2.66)	0.399	1.01 (0.47–2.15)	0.987

Each of four factors depicted was included into own model, along with the following covariates: age ≥65 years, male gender, current smoking, body mass index ≥30 kg/m^2, raised blood pressure, LDL ≥2.5 mmol/L, inadequate glycemic control, atrial fibrillation, treatment with ACEi or ARBs, treatment with statins, treatment with warfarin and brain natriuretic peptide >100 ng/mL *plus* SF-36 score ≤40 in model B

[odds ratio (95 % CI) 10.99 (4.91–24.57)]. Post-stroke anxiety (PSA) has to date been given much less attention than PSD, but it seems to be a longer time consequence of stroke and more typical for chronic phases. A study reported that PSA developed in about 24 % of patients 6 months after the stroke event [29]. Indeed, HADS questionnaire is not an appropriate instrument to make a formal diagnosis of anxiety or depression but more-than-less only screening tool for anxious/depressive mood disorders.

Our study has several limitations. First, the information about the cause of death is primary based on ICD-10 codes declared in death certificates and were adjudicated using only available medical documentation. As several patients died at home, we were not able to ascertain every death cause. Therefore, the cardiovascular mortality rate (but not the all-cause mortality) may be biased (overestimated). Further, we did not have full information on non-fatal vascular events during follow-up. Specifically, the incidence of recurrent stroke may be interesting but is currently unavailable for technical reasons. Presence of aphasia or cognitive impairment as consequence of stroke might also potentially influence the reliability of SF-36 or HADS questionnaires (despite that real prevalence of these disorders was rather low in our sample). Several data were not a part of examination protocol, being only extracted from hospitalization records (namely modified Rankin score), and therefore, their reliability can be also potentially influenced. Inherent limitation of the statistical methods employed is that complex relationships between multiple variables may potentially mask an interaction that appears to be independent but could still be related to some other factor (or multiple factors).

Our series also consisted of relatively less-affected post-stroke patients. The most complicated patients died before interview (about 46 %), and we can only speculate that the majority of living non-responders did not attend the interview because of their very poor general health condition. On the other hand, the fact that our series included less-affected patients with a still existing potential for secondary prevention should strengthen the practical utility of our results.

Conclusions

In our sample of well-stable patients at least 6 months after their first-ever ischemic stroke, we have confirmed the presence of anxiety and depression as the most important predictors of QoL and well-being. However, our study is the first to demonstrate QoL relation to only subclinically increased BNP. Indeed, in the setting of stable, only mildly or moderately affected, post-stroke patients' impaired QoL (quantified as total SF-36 score) represents an independent surrogate of mortality risk.

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Conflicts of Interests None.

Compliance with Ethical Standards All procedures performed in the study were in accordance with the Good Clinical Practice principles and ethical standards by 1964 Helsinki Declaration and its later amendments. Local Ethical Committee of the University Hospital in Pilsen approved

the study protocol. Written informed consent was obtained from all individual participants included in the study. The data were stored and evaluated under the provisions of the Czech Data Protection Act. The authors declare that they have no conflict of interest.

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The Obesity Paradox and Survivors of Ischemic Stroke

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Background: Although obesity is a risk factor for stroke and achieving normal weight is advocated to decrease stroke risk, the risk associated with obesity and weight loss after stroke has not been well established. The aim of this study was to assess the association of obesity at the time of stroke admission and weight loss after stroke with total mortality. *Methods:* We analyzed 736 consecutive patients (mean age, 66 ± 11 years; 58% men) hospitalized for their first ischemic stroke. Body weight at hospital admission and at the outpatient visit during follow-up was used in the analysis. *Results:* After multivariate adjustment, obesity at admission was associated with lower mortality risk as compared with normal weight (hazard ratio [HR], .50, $P = .03$). At the outpatient visit, with a median follow-up time of 16 months, 21% of patients had lost more than 3 kg of weight. Stroke severity, heart failure, transient ischemic attack, and depression after stroke were independently associated with significant weight loss. Weight loss of more than 3 kg was associated with increased mortality risk (HR, 5.87; $P = .001$) independently of other factors. Similar results were seen when weight loss was defined as losing more than 3% of baseline weight (HR, 4.97; $P = .004$). Weight gain of more than 5% of the baseline weight tended to be associated with better survival when compared with no weight change (log-rank test, $P = .07$). *Conclusions:* Normal weight at hospital admission and weight loss after ischemic stroke are independently associated with increased mortality. Overweight and obesity at baseline do not decrease the risk associated with weight loss. **Key Words:** Ischemic stroke—obesity—weight loss—outcome—mortality.

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Obesity is a well-recognized risk factor for stroke.[1,2] The risk associated with obesity is partially explained by obesity-related cardiovascular risk factors as hypertension, diabetes, and dyslipidemia.[3,4] Achieving normal weight (body mass index [BMI], 22.5-24.9 kg/m^2) is advocated to decrease the risk of stroke.[5,6] However, previous data have shown inconsistent results when testing the association between obesity and poststroke mortality. Several studies in patients after stroke have shown lower mortality risk in overweight/obese subjects as compared with normal weight,[7-11] whereas others have shown increased[12,13] or similar[14] risk associated with obesity. Guidelines on secondary prevention after stroke recommend weight control to improve obesity-related risk factors and to reduce adverse outcomes.[15,16] On the other hand, the study by Jonsson et al,[16] suggests that significant weight loss in the first 4 months after stroke is associated with increased risk of mortality, although the study did not test whether weight loss after a longer period since the index event is also associated with increased mortality risk.

The aim of the present study was to assess the association of obesity at the time of stroke admission and weight loss after stroke with total mortality among patients after their first ischemic stroke and to determine, if such an association exists, whether it could be explained by comorbidities causing weight loss in chronic conditions.

Methods

Study Population

All consecutive patients aged 18-80 years hospitalized at Thomayer Hospital, Prague, or Charles University Medical and University Hospital, Pilsen, Czech Republic, for their first-ever ischemic stroke between March 2009 and January 2012 were eligible for this study. Because both of these hospitals are the only stroke centers in the specific region, all the patients with a stroke in the community were admitted to these hospitals. Stroke was defined as focal neurologic symptoms lasting more than 24 hours, consistent with the original World Health Organization criteria,[17] unless thrombolytic therapy was applied. Discharge diagnoses were used to confirm the diagnosis. Patient characteristics on hospital admission/during hospitalization for acute stroke were retrospectively retrieved from their medical records. The BMI on hospital admission was calculated dividing the body weight in kilos by the squared height in meters. Significant weight loss was defined as weight loss of more than 3 kg, as previously used.[16] Furthermore, weight loss was also defined as percentage of baseline weight (>3%), using the 25th percentile of weight change as the cutoff. Homologated electronic scale and wall-mounted stadiometer were used to measure body weight and height at the time of outpatient visit, respectively. The subtype of acute ischemic stroke was classified using a validated computerized algorithm for etiologic classification of ischemic stroke (Causative Classification of Stroke System[18]). The neurologic severity on admission was assessed by the National Institute of Health Stroke Scale score. Functional status at discharge was assessed using the bladder, transfer, and walking items from the Barthel index. Summary score of these items at the time of discharge is provided. All eligible patients were invited for 1 outpatient visit 6 months to 3 years after the index event. Disability at the time of visit was assessed using the Barthel index and modified Ranking Scale, anxiety and depression using the Hospital Anxiety and Depression Scale (HADS). Some previous findings from this patient's cohort have been previously reported,[19,20] but the present study findings regarding the impact of obesity and weight reduction on mortality after stroke have not been reported. The study was approved by the joint local ethics committee of the Institute for Clinical and Experimental Medicine and Thomayer Hospital, Prague, Czech Republic.

Clinical Outcome

The primary outcome was total mortality, and it was assessed from General Health Insurance Company registry that keeps, by law, a list of all people insured and all deaths in the Czech Republic. As health insurance is mandatory by law for all Czech citizens and is paid for by the employer/employee, or by the government (for children, retired, and unemployed persons), the databases of the General Health Insurance Company registry and the National Population Registry are basically identical.

Statistical Analysis

Descriptive statistics are given as mean ± standard deviation, median (interquartile range [IQR]), or frequency and percent. Differences between patient groups in continuous variables were assessed by analysis of variance with Tukey's post hoc test and independent sample *t* test if normally distributed or with the Kruskal–Wallis and Mann–Whitney test for non-normally distributed variables. Differences in frequencies were compared by the χ^2 test or Fisher exact test in case of small expected frequencies. Patients were grouped into 3 groups by BMI at hospital admission: normal-weight group (BMI <24.9), overweight group (BMI = 25-29.9), and obese group (BMI ≥30). The normal BMI group was used as the reference group. BMI below 18.5 is considered the cutoff for malnutrition. Because there was only 1 patient below this cutoff value, we did not separate this group from the normal-weight group. Kaplan–Meier survival curves and log-rank test were used to compare differences in mortality risk among BMI categories and weight-loss groups. To determine whether BMI categories and weight loss are associated with mortality risk independently of other factors, Cox proportional hazard model was used.

Factors associated with mortality in univariate Cox model and factors with effect on mortality proven in previous studies among patients after stroke were included into the multivariate model. The proportional hazards assumption was tested using Schoenfeld residuals. Calculations were performed using SPSS 19 software (Chicago, IL). A two-sided *P* value less than .05 was considered to be statistically significant.

Results

Among 736 patients (mean age, 65.7 ± 10.5 years; 58% men) hospitalized for their first-ever ischemic stroke between March 2009 and January 2012 at the 2 study centers, data on BMI at the time of hospital admission were missing in 225 patients, leaving 511 subjects with BMI data. From these, 112 patients (21.7%) had normal BMI, 194 (37.6%) were overweight, and 205 (39.7%) had obesity. Among the obese, 136 (66%) had mild (BMI, 30-34 kg/m2), 49 (24%) moderate (BMI, 35-39 kg/m^2) and 20 (10%) severe obesity. Descriptive statistics according to BMI at the time of hospitalization are provided in Table 1.

By January 2014, 161 patients (21.9% of the total cohort) had died, of which 144 (19.6%) died before the outpatient visit. In total, 424 patients (70% of all eligible patients) were examined after a median follow-up of 16 months (IQR, 10-28) after the index event. Of these, 351 had weight data both at the time of hospitalization and at the outpatient visit. These patients were followed for a median of 21 months (IQR, 19-23) until January 2014.

Table 1. *Descriptive statistics by admission body weight*

Variables	Normal (n = 112)	Overweight (n = 194)	Obese (n = 205)	Total (n = 511)	*P* value
Age (y)	63.25 ± 13.46	66.08 ± 9.96	64.42 ± 9.65	64.79 ± 10.74	.07
Sex (male)	58 (52)	132 (68)*	115 (56)†	305 (60%)	.008
Body mass index (kg/m^2)	22.92 ± 1.93	27.58 ± 1.36*	34.43 ± 4.31*†	29.31 ± 5.44	<.001
Height (cm)	167.46 ± 8.42	168.91 ± 9.34	167.55 ± 9.79	168.08 ± 9.39	.40
Admission systolic BP (mm Hg)	149 ± 24	155 ± 27	157 ± 27*	155 ± 26	.04
Admission diastolic BP (mm Hg)	85 ± 14	86 ± 14	90 ± 14*†	88 ± 14	.003
Discharge systolic BP (mm Hg)	128 ± 16	135 ± 16*	137 ± 19*	134 ± 18	.001
Discharge diastolic BP (mm Hg)	75 ± 11	78 ± 10	81 ± 11*†	78 ± 11	<.001
Total cholesterol (mmol/L)	5.01 ± 1.11	5.05 ± 1.24	5.25 ± 1.67	5.12 ± 1.41	.25
LDL cholesterol (mmol/L)	3.02 ± .97	3.09 ± .96	3.21 ± 1.15	3.12 ± 1.04	.35
HDL cholesterol (mmol/L)	1.46 ± .42	1.35 ± .40	1.26 ± .36*	1.34 ± .39	.001
Triglycerides (mmol/L)	1.18 (.89-1.79)	1.30 (.96-1.90)	1.57 (1.18-2.30)*†	1.4 (1.00-2.01)	<.001
Glucose at admission (mmol/L)	6.79 ± 2.40	7.45 ± 3.20	8.07 ± 3.92*	7.55 ± 3.39	.005
Comorbidities					
Hypertension, n (%)	61 (55)	153 (79)*	173 (85)*	387 (76)	.001
Diabetes, n (%)	15 (13)	55 (28)*	71 (35)*	141 (28)	.001
Dyslipidemia, n (%)	45 (40)	49 (49)	102 (50)	242 (47)	.20
Atrial fibrillation, n (%)	13 (12)	21 (11)	31 (15)	65 (13)	.56
Prior myocardial infarction, n (%)	8 (7)	19 (10)	23 (11)	50 (10)	.48
Coronary bypass surgery n (%)	5 (5)	14 (7)	9 (5)	28 (6)	.38
Percutaneous coronary intervention, n (%)	5 (5)	14 (7)	5 (3)	24 (5)	.15
Stroke subtype					.42
Atherosclerosis, n (%)	14 (13)	36 (19)	25 (12)	75 (15)	
Cardioembolism, n (%)	37 (33)	51 (26)	66 (32)	154 (30)	
Lacunar, n (%)	13 (12)	25 (13)	29 (14)	67 (13)	
Other, n (%)	8 (7)	9 (5)	6 (3)	23 (5)	
Undetermined, n (%)	40 (36)	73 (38)	79 (39)	192 (38)	
NIHSS at admission	4 (2-7)	4 (2-7)	4 (2-7)	4 (2-7)	.23
Barthel index	40 (40-40)	40 (35-40)	40 (35-40)	40 (35-40)	.94
Reperfusion therapy, n (%)	19 (17)	36 (19)	34 (17)	89 (17)	.87
Discharged home, n (%)	75 (67)	150 (77)	152 (74)	377 (74)	.14

Abbreviations: BP, blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NIHSS, National Institutes of Health Stroke Scale.

NIHSS assessed at the stroke admission.

Barthel—urinary, transfer, and mobility components of the Barthel index of performance in activities of daily living at discharge.

*$P < .05$ versus normal

†$P < .05$ versus overweight

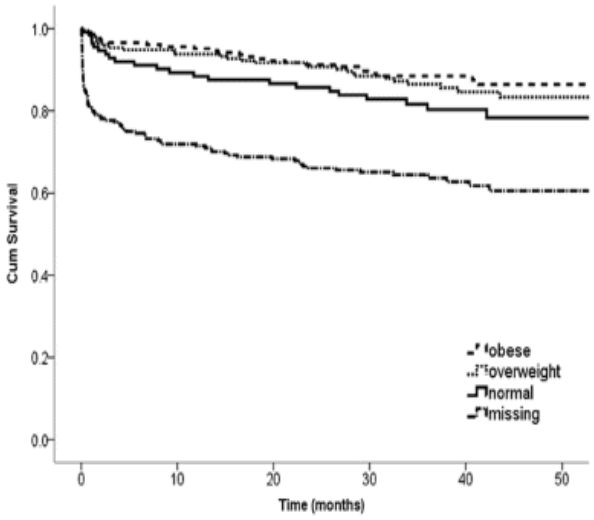

Figure 1. *Kaplan–Maier survival curve by body mass index categories.*

No at risk

Normal BMI	112	100	97	81	47	15
Overweight	194	181	177	149	82	42
Obese	205	196	189	157	91	35
Missing	225	161	152	118	63	17

During this period, 15 patients with complete weight data (4.3%) died. Figure S1 in Appendix shows the study flow chart.

Obesity and Mortality after Stroke

Subjects with missing BMI had more severe stroke and worse functional status at the time of hospital admission as compared with groups with available BMI (Table S1 in Appendix). Obese subjects had higher blood pressure, triglycerides, glucose, and higher prevalence of hypertension and diabetes as compared with normal-weight individuals (Table 1). There was no difference in stroke severity or functional status at the time of admission between the BMI groups. In the unadjusted analysis, there was a trend toward higher mortality in the normal-weight group as compared with the obese group (log-rank test, $P = .07$), whereas subjects with missing weight had the worst survival as compared with all other groups ($P < .001$ by log-rank test; Fig 1). After adjustment for multiple confounding factors, obesity was associated with better survival as compared with normal weight (hazard ratio [HR], .50; 95% confidence interval [CI], .27-.93; $P = .03$), whereas there was no difference between the group with missing BMI at the time of hospitalization and normal-weight group (HR, 1.03; 95% CI, .60-1.78, $P = .91$; Table 2).

Weight Loss and Mortality after Stroke

In total, 73 of 351 (21%) patients had weight loss higher than 3 kg during the median time of 16 months after the stroke event. At the time of outpatient visit, 29% of patients with weight loss after stroke reported willingness to lose weight. In the univariate analysis, subjects with significant weight loss had more severe stroke at the time of hospital admission, worse functional status at the time of hospital discharge and at the time of outpatient visit, and more often had history of heart failure and transient ischemic attack (TIA) after the stroke event and higher score of the HADS depression questionnaire at the time of outpatient visit (Table S2 in Appendix). In the multivariate analysis, history of TIA after stroke, history of heart failure, overweight, more severe stroke, and higher HADS depression score were independently associated with significant weight loss (Table S3 in Appendix). If significant weight loss was defined by weight decrease of more than 3% of the baseline body weight (which represents the 25th percentile in the population), factors independently associated with weight loss did not change. Significant weight loss was associated with worse survival (log-rank test, $P < .001$; Fig 2). On the other hand, weight gain of more than 5% (75th percentile of weight change percentage in the population) tended to be associated with better survival than no significant weight change (25th-75th percentile; log-rank test, $P = .07$). Because of small sample size, group with weight gain was further analyzed together with the group without significant weight change. In the multivariate model, significant weight loss remained independently associated with worst survival (HR, 5.87; 95% CI, 1.98-17.40; $P = .001$), whereas baseline BMI was not associated with

Table 2. *Cox regression analysis of factors associated with total mortality after the first ischemic stroke*

Variables	HR	95% CI	*P* value
Obesity groups			
Normal	1	reference	
Overweight	.61	.33-1.12	.11
Obese	.50	.27-.93	.03
Missing	1.03	.60-1.78	.91
Age	1.04	1.01-1.06	.002
Sex	.50	.34-.74	.001
Reperfusion therapy	.43	.25-.73	.002
Stroke severity			
NIHSS <6	1	reference	
NIHSS 6-8	1.43	.79-2.61	.24
NIHSS ≥8	3.07	1.74-5.43	<.001
Barthel<35	1	reference	
Barthel 35-40	.08	.01-.55	.11
Barthel 40	.31	.20-.47	<.001
Comorbidities			
Hypertension	1.03	.64-1.67	.9
Diabetes	2.01	1.36-2.96	<.001
Dyslipidemia	1.54	1.06-2.24	.02
Stroke subtype			
Lacunar	1	reference	
Atherosclerosis	.82	.37-1.82	.62
Cardioembolism	1.25	.63-2.48	.52
Other/undetermined	.98	.49-1.93	.94

Abbreviations: CI, confidence interval; HR, hazard ratio; NIHSS, National Institutes of Health Stroke Scale.

NIHSS assessed at the stroke admission.

Barthel—urinary, transfer, and mobility components of the Barthel index of performance in activities of daily living.

mortality (Table 3). When significant weight loss was defined as weight loss of more than 3% of the weight at the time of index event hospitalization, 7 (12%) patients with normal weight, 40 (29%) overweight, and 39 (26%) obese at the time of hospitalization had significant weight loss. In the multivariate analysis, weight loss of more than 3% remained independently associated with increased mortality (HR, 4.97; 95% CI, 1.65-14.94; $P = .004$; Table S4 in Appendix). When multivariate analysis was stratified by baseline BMI category, weight loss of more than 3% was associated with mortality risk in obese (HR, 5.54; 95% CI, 1.12-27.48; $P < .05$) and overweight (HR, 26.53; 95%. CI, 1.54-457.57; $P < .05$), but not in subjects with normal baseline weight (HR, .10; 95% CI was infinity; $P = .99$).

Discussion

In the present study among patients hospitalized for their first ischemic stroke, we show that (1) obesity is associated with lower mortality as compared with normal weight, (2) stroke severity, heart failure, TIA, and depression after stroke are associated with weight loss, (3) significant weight loss is associated with increased mortality risk independently of other factors, and (4) overweight and obesity at baseline do not decrease the long-term mortality risk associated with weight loss.

Our findings confirm and extend previous findings on the relationship of obesity and weight loss with mortality risk (obesity paradox) in patients after stroke, myocardial infarction, and with heart failure.[21-25] Several previous studies in patients after stroke have shown lower mortality risk in overweight/obese subjects as compared with normal weight,[7-9] whereas others have shown increased risk associated with obesity.[12,13] Among patients after their first ischemic stroke, Vemmos et al[7] observed a reduced mortality in overweight (−18%) and obese (−29%) patients when compared with the normal-weight group. Similarly, in a Danish stroke registry,[9] overweight (−27%) and obesity (−16%) were associated with better survival when compared with normal-weight patients. Recently, Doehner et al,[8] have shown among patients with stroke or TIA lower mortality risk in overweight (−14%) and obese (−24%) as compared with normal weight. The difference in the magnitude of mortality risk in overweight (−39%) and obese (−50%) seen in our study when compared with previous studies can be explained by differences in study populations. We included only subjects after ischemic stroke, whereas previous studies included also subjects with hemorrhagic stroke. Recent studies have shown that overweight/obesity increase mortality after hemorrhagic stroke.[26] Thus, combining ischemic and hemorrhagic stroke may blunt the association between overweight/obesity and stroke mortality. This can also explain the increased mortality risk after stroke by obesity in Asian counties,[12,13] in which hemorrhagic stroke is more common than in Western populations and accounts for up to 50% of all strokes in China.[27]

Mechanisms of the protective effect of increased BMI among patients with ischemic stroke are still not fully understood. A significant limitation of BMI is its failure to differentiate between an elevated body fat content and preserved or increased lean mass. Body composition as a function of lean mass could explain the obesity paradox.[24,28] Increased muscle mass and muscular strength is associated with better cardiovascular prognosis and survival.[29] In the future, studies assessing the influence of fat mass and lean mass on survival in ischemic stroke will be needed.

Another important finding from our study is that weight loss even after a longer period since the ischemic stroke is independently associated with increased mortality risk. This finding extends the results from the Lund Stroke Register,[16] in which significant weight loss in the early period after ischemic stroke (in the first 4 months) was more common in patients who ultimately died during the first year after stroke than in survivors. However, the independent association of weight loss after stroke

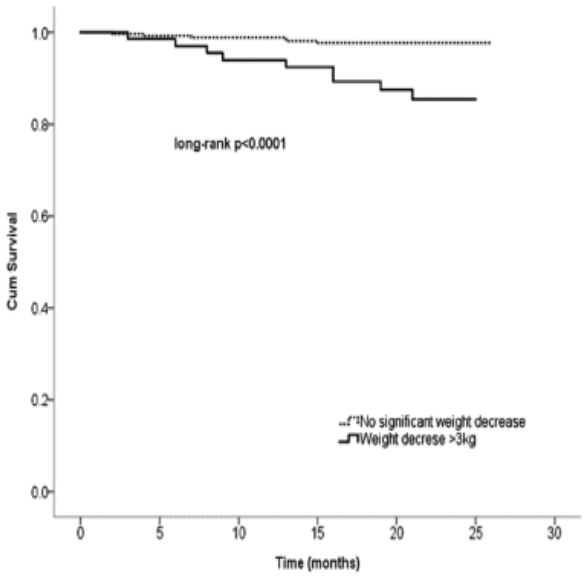

Figure 2. *Kaplan–Maier survival curve by weight change categories.*

No at risk

No weight loss	278	256	255	251	192	9
Weight loss	73	64	61	59	41	0

with stroke mortality in population-based groups of stroke survivals has never been tested before. Thus, the present study is the first one to show that weight loss after stroke is independently associated with increased mortality. Because the prevalence of malnutrition decreases steeply with time from stroke,[30] it is noteworthy that weight loss evaluated also after a longer period since the index event (median time since the index event was 16 months) increases mortality risk. We observed that almost a quarter of all patients after first ischemic stroke have significant weight loss (>3 kg), in line with previous findings.[16] Interestingly, significant weight loss expressed as percentage of the baseline weight was less common in normal weight as compared with overweight and obese groups ($P < .05$ for all), suggesting that the results were mainly driven by weight loss among overweight and obese subjects, as confirmed when analyses were stratified by baseline BMI. Thus, despite the common perception that normal-weight patients will be particularly those at increased risk of weight-loss–associated mortality as compared with overweight/obese groups, our results showed that the long-term risk associated with weight loss cannot be underestimated in overweight/obese groups. However, we cannot exclude that normal-weight individuals with significant weight loss were more prone to die before the study visit.

Table 3. *Cox regression analysis of factors associated with total mortality after the study visit*

Variables	HR	95% CI	*P* value
Weight loss >3 kg	5.87	1.98-17.40	.001
Hypertension	3.50	.37-33.51	.27
Diabetes	2.99	.98-9.09	.05
Heart failure history	9.14	1.40-59.85	.02
NIHSS tertiles			
<6	1	reference	
6-8	<.01		.98
≥8	.99	.25-4.98	.99
Barthel index >90	.87	.18-4.21	.86
BMI visit			
Normal	1	reference	
Overweight	1.08	.24-4.90	.92
Obesity	.97	.24-4.00	.97

Abbreviations: BMI, body mass index; CI, confidence interval; HR, hazard ratio; NIHSS, National Institutes of Health Stroke Scale.
NIHSS assessed at the stroke admission.
Data are adjusted for age, sex, and time since the index event.

In our study, severity of stroke along with significant comorbidities such as heart failure, TIA, and depression was associated with weight loss. This finding has some implications supporting the role of monitoring weight change and nutritional status in patients with more severe stroke.

Limitations

The major limitation of the present study is that we cannot differentiate intentional weight loss from weight loss caused by comorbidities. In patients with coronary artery disease, observational weight loss is associated with increased adverse cardiovascular events, whereas

intentional weight loss is associated with lower clinical events.[31] In the present study, 29% of patients with weight loss reported willingness to lose weight, whereas there was no difference in the willingness to lose weight between subjects with and without significant weight loss. Because several comorbidities and not weigh loss intention were independently associated with weight loss, we may assume that the observed weight loss was nonintentional and mainly driven by comorbidities. Furthermore, we cannot exclude that observed inverse associations between BMI and poststroke survival may have resulted from unaccounted confounders. Future studies assessing the effect of intentional weight loss on mortality after stroke will help to elucidate the role of weight loss in this clinical setting.

In this study, data on weight and height were retrospectively collected from medical records, what is likely less accurate than rigorously controlled methods and may therefore have underestimated any true difference between groups. Furthermore, a large proportion of patients at hospital admission had missing weight. Presumably, the most common cause of missing weight was more severe stroke and inability to stand up. These patients also had higher mortality risk in the unadjusted analysis, whereas after adjustment the risk was comparable to other weight groups, suggesting that more severe stroke is responsible for increased mortality risk in this group.

Conclusions

When compared with obesity, normal weight at the time of hospital admission is associated with increased mortality after the first ischemic stroke. Significant weight loss, either short or long term since the index event, is associated with increased mortality too. Overweight and obesity at baseline, both factors linked to better survival in this cohort, did not decrease the long-term risk associated with weight loss.

Supplementary Data

Supplementary data related to this article can be found online at http://dx.doi.org/10.1016/j.jstrokecerebrovasdis.2015.03.008.

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Tobacco smoking strongly modifies the association of prothrombin G20210A with undetermined stroke: Consecutive survivors and population-based controls

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ABSTRACT

Objective: Due to contradictory results of previous studies evaluating the association between ischemic stroke (IS) and thrombophilic polymorphisms, their routine screening in IS patients, particularly those older than 60 years, is not recommended. We evaluated the differences in the distribution of rs6025 and rs1799963 polymorphisms according to IS subtypes and their interaction with smoking.

Methods: We conducted a case–control study of 423 hospital-based consecutive survivors of their first-ever IS and 614 population-based controls. Survivors (18–81 years) with IS documented by brain imagining were examined at a median of 16 months after the index event. The stroke subtype was categorized using the Causative Classification of Stroke System. Controls (50–75 years) were free of a history of stroke/TIA, coronary heart disease, and venous thromboembolism.

Results: Age- and gender-adjusted prevalence of individuals carrying at least one copy of the rs1799963A minor allele was 5.3% among stroke survivors (by subtypes: 3.1% in large artery atherosclerosis, 2.0% in cardio-aortic embolism, 2.4% in small artery occlusion, and 10.3% in undetermined stroke) vs. 2.4% among controls. In multinomial multivariate adjusted analysis, rs1799963 was exclusively associated with undetermined stroke (OR: 3.67; 95% CI: 1.52–8.85; $p = 0.004$). There was strong evidence of rs1799963 × smoking synergistic interaction (OR: 5.14; 95% CI: 1.65–16.01; $p = 0.005$). There was no association of rs6025 with IS in general, or with any subtype.

Conclusions: In our consecutive IS survivors, carriage of the rs1799963A allele is associated with undetermined stroke. This effect appears to be confined to smokers.

1. Introduction

G to A transitions at nucleotide position 1691 in the Factor V gene (Arg506Gln; rs6025) and at nucleotide position 20210 in the 3′-untranslated region of the Prothrombin gene (G20210A; rs1799963) represent more than a half of the hereditary thrombophilic states [1]. Whereas their role in venous thromboembolism is clearly established, the findings from studies of ischemic stroke (IS) in general are inconclusive. A few meta-analyses showed a weak-to-modest association of rs6025 and rs1799963 with stroke, typically enhanced by other pro-coagulant risk factors such as cigarette smoking [2,3]. Given the only modest associations reported in case–control studies, the lack of evidence supporting the causality, and no clear-cut treatment guidelines, routine screening for thrombophilic polymorphisms in stroke patients, particularly

Abbreviations: BMI, body mass index; eGFR, estimated glomerular filtration rate; IS, ischemic stroke; PFO, patent foramen ovale; SSS-TOAST, Trial Org 10172 in Acute Stroke Treatment; EQA, external quality assessment; IQC, internal quality control.

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0021-9150/

those older than 60 years, is not recommended. However, genetic testing could be informative in patent foramen ovale (PFO)-related and young-onset strokes [4,5].

Because of the heterogeneous pathophysiology of IS, classification into different subtypes has been advised in genetic association studies. The SSS-TOAST (Trial Org 10172 in Acute Stroke Treatment) classification of IS distinguishes five major subtypes differing in prevalence, risk factors, further management and prognosis: 1. large artery atherosclerosis, 2. cardio-aortic embolism, 3. small artery occlusion, 4. other determined causes, and 5. undetermined causes [6]. Only a few research groups have addressed the selective role of hereditary thrombophilia in a particular stroke mechanism reporting conflicting results. While the majority of case–control studies focused on PFO-related stroke in young adults [4,7], only few included elderly individuals. Studies involving individuals over 60 years were either underpowered to detect an association with the stroke subtypes, or focused only on one or two subtypes [8–13]. None of them included a population-based control group, nor performed interaction analysis between polymorphisms and tobacco smoking.

The aim of the present study was to evaluate the distribution of rs6025 and rs1799963 polymorphisms among consecutive IS survivors at large, and by stroke subtypes. The differences in the distribution of thrombophilic polymorphisms were compared with population-based controls. Furthermore, interactions between carriage of at least one copy of the respective minor allele and smoking habits were tested.

2. Materials and methods

2.1. Cases

All consecutive patients admitted to Thomayer Hospital in Prague or Charles University Hospital in Pilsen, Czech Republic, for their first-ever acute IS between May 2009 and January 2012, were approached for consent to participate in this survey [14]. Patients 18–81 years old, with duration of symptoms > 24 h (unless thrombolysis was applied), in whom CT or MRI had excluded hemorrhagic stroke, were eligible [15]. Of the 736 qualified patients, 424 were recruited in this study; 128 patients died during hospitalization for the index event or during the period between their discharge and examination (response rate, 69.7%). One patient was excluded from the final analyses due to missing data. Survivors were examined at 6 months to 3 years after the event hospitalization (median time, 16 months).

Baseline demographic and anthropometric data, a history of cardiovascular risk factors, atrial fibrillation, previous cardiovascular events, and detailed drug treatment were obtained. The examination protocol included a resting electrocardiogram, laboratory tests (renal function, fasting lipid profile, and plasma glucose), morning spot urine collection, and carotid ultrasound. Blood pressure was measured by a digital automatic blood pressure monitor (Omron M10-IT, OMRON HEALTHCARE Co., Ltd, Kyoto, Japan) in the right arm in triplicate. In patients with atrial fibrillation or frequent extrasystoles, standard mercury sphygmomanometers with correctly sized cuffs were used. The mean of the 2nd and 3rd readings was retained. The results of the tests performed during the index hospitalization (brain CT or MRI, transthoracic or transesophageal echocardiography, carotid ultrasonography, electrocardiogram, and ambulatory electrocardiogram) were retrospectively retrieved from the medical records. Ischemic stroke subtype was categorized by two blinded physicians certified in the validated Causative Classification of Stroke System (a computerized algorithm based on the original SSS-TOAST classification) [6]. Agreement on stroke categorization was reached in 89% of patients and disagreements were re-evaluated.

2.2. Controls

Controls (n = 614) were specifically selected for this case group from 1337 participants of the Czech post-MONICA study (2007–2009), residing in Prague East and Pilsen districts (regions corresponding to the catchment areas of Thomayer Hospital in Prague and Charles University Hospital in Pilsen). Only individuals aged 50–75 years, free of a history of stroke/transient ischemic attack (TIA), coronary heart disease, any surgical revascularization, and thromboembolism were eligible. The Czech post-MONICA study is a cross-sectional survey of cardiovascular risk factors in a 1% population sample from nine Czech districts randomly selected from the General Health Insurance Company registry. Demographic and anthropometric data, a history of cardiovascular risk factors, previous cardiovascular events, and current drug treatment were obtained as described in detail elsewhere [16]. A sample of 12-h fasting blood and an early morning spot urine sample were collected. Blood pressure was measured according to the current guidelines of European Society of Hypertension and of European Society of Cardiology [17].

Both studies were approved by the ethics committee of the Institute for Clinical and Experimental Medicine and Thomayer Hospital, Prague, Czech Republic and all participants provided their informed consent.

2.3. Laboratory analyses

Biochemical analyses of serum lipids and creatinine, fasting plasma glucose, and urinary albumin, and creatinine excretion were performed in a central core laboratory, with Centers for Disease Control and Prevention (Atlanta, GA, USA) continuously monitoring the accuracy of analyses [18]. Urinary albumin and creatinine excretion were determined using immunoturbidimetry in an early morning spot urine sample, and the albumin/creatinine ratio was calculated. To estimate glomerular filtration rate (eGFR), the Chronic Kidney Disease Epidemiology Collaboration equation was used [19].

The standardized operating procedures were applied in stroke survivors and controls (described in detail elsewhere) [20]. Genomic DNA was extracted from peripheral blood leucocytes by means of a MagNA Pure LC Nucleic Acid Extraction System™ with a MagNA Pure DNA Isolation Kit I™ (Roche Diagnostics, Mannheim, Germany). The rs6025 and rs1799963 genotypes were determined using a real time polymerase chain reaction (PCR) in a process called fluorescence resonance energy transfer (FRET) on a LightCycler® 480 System with LightCycler® 480 Genotyping Master kits (Roche Diagnostics, Mannheim, Germany). Specific primers and fluorescently labeled probes were custom-made in cooperation with TIB MOLBIOL, Berlin, Germany. All molecular genetic tests were performed in the Central Laboratory for Hematology and Thrombotic Centre of the First Medical School of Charles University in Prague and the General Teaching Hospital using certified methods. Laboratory staff was unaware of the characteristics of the participants. All methods were subject to the annual external quality assessment (EQA) at regular quality control performed by the Institute for Standardization and Documentation in Medical Laboratories (INSTAND, Düsseldorf, Germany), and internal quality control (IQC). IQC involved assessment of repeatability and intermediate precision of the measurement, as well as of addition of a control sample with a known heterozygous genotype and a negative control in every run.

2.4. Definition of phenotypes

Carriage of the rs6025 and rs1799963 polymorphisms was defined as the presence of the respective minor (A) allele either in

heterozygous or homozygous form (GA or AA). Individuals were considered smokers, if they reported regular tobacco consumption ever before the index hospitalization. Increased alcohol intake before the index event was defined as > 168 g/week in men and >112 g/week in women. Education was defined by the highest acquired level (basic, secondary, or university). Hypertension was diagnosed when the visit blood pressure was ≥140/90 mmHg, or if treated with blood pressure-lowering medication [21]. Hyperlipidemia was defined as visit total cholesterol ≥ 5 mmol/l, or LDL-cholesterol ≥ 3 mmol/l, or HDL-cholesterol < 1 mmol/l in males and <1.3 mnol/l in females, or triglycerides > 1.7 mmol, or current use of lipid-lowering medication. Individuals were considered diabetic if their fasting plasma glucose was 7.0 mmol/l or greater, or if they used glucose-lowering medication [22]. Elevated albuminuria was defined as an albumin/creatinine ratio ≥ 1.9 mg/mmol in men, and ≥2.8 mg/mmol in women [23]. Individuals were supposed to have chronic kidney disease if their eGFR was <60 ml/min/1.73 m^2 [19].

2.5. Statistical analysis

The two-tailed t-test for independent samples and one-way analysis of variance with Tukey's post-hoc test were used to compare the differences in age among the patient groups and controls where applicable. The distribution of gender was compared by Pearson's chi-square test. The age- and gender-adjusted prevalence of clinical and genetic characteristics was calculated by weighted average of age- and gender-specific rates. The differences in the distribution of clinical and genetic characteristics between groups were compared by age- and gender-adjusted logistic regression. The differences in the distribution of genetic characteristics were further adjusted for all the potential confounders. Odds ratios with 95% confidence intervals were calculated using the presence of IS as a dependent variable. BMI was logarithmically transformed to normalize variable distribution.

The clinical and genetic characteristics by IS subtypes and control individuals were compared using generalized linear models adjusted for age and gender. To test the association between IS subtypes and studied polymorphisms, we performed a multinomial regression analysis using IS subtypes as dependent variable and control group as a reference category.

In this study, only one homozygote of rs1799963 (stroke survivor) and 4 homozygotes of rs6025 (2 survivors, and 2 controls) were identified, which makes testing the interaction between count of the respective A alleles and smoking unreasonable. Instead, pre-specified interaction terms between smoking and carriage of at least one copy of the respective A allele (rs1799963, rs6025; regardless of homozygosity or heterozygosity) were tested in multivariate adjusted logistic regression. Confounders were added in a step-wise manner including the respective polymorphism and smoking status per se. The odds ratio of undetermined stroke was calculated according to smoking status and carriage of the rs1799963A allele, using non-smokers non-carriers as reference category, and adjusting for other cardiovascular risk factors. Covariates were added in a step-wise fashion, where applicable.

Our study achieves a power of 96% with a type I error of 5% to detect an odds ratio of IS at large of 2.0, assuming a frequency of genotype of 2.4% among controls and using a two-sided two-sample z-test. In subtype analysis, our study achieves a power of 82% with a type I error of 0.0125 (Bonferroni-corrected) to detect a small effect size w of 0.13 and using a χ^2 test with a degree of freedom of 4.

Statistical analysis was performed using SPSS 16 software (SPSS Inc., Chicago, Illinois, USA). When comparing IS survivors at large with controls, a significant difference was defined as a two-sided p value <0.05. In subtype analysis, a Bonferroni-corrected significant difference was defined as a two-sided p value <0.0125 (Tables 3 and 4).

3. Results

The age- and gender-adjusted prevalence of cardiovascular risk factors among stroke survivors at large and controls are summarized in Table 1. Stroke survivors were more often exposed to all cardiovascular risk factors compared with controls, except for alcohol intake.

3.1. Distribution of the rs6025 and rs1799963 polymorphisms in IS survivors at large and controls

The frequencies of rs6025 and rs1799963 genotypes in controls were in Hardy–Weinberg equilibrium (p = 0.469; p = 0.759, respectively). Among the 423 stroke survivors, 44 carried rs6025 (2 in homozygous form), and 22 carried rs1799963 (1 in homozygous form). Of the 614 controls, 53 carried rs6025 (2 in homozygous form), and 15 carried rs1799963 (all in heterozygous form). As the homozygous genotypes had a low prevalence, which did not differ between the groups, carriage of at least one copy of the respective minor allele was used in further analyses.

The count and the age- and gender-adjusted prevalence of rs6025 and rs1799963 polymorphisms among stroke survivors and controls are presented in Table 2. The distribution of rs6025 did not differ between the groups. In contrast, stroke survivors were approximately twice more often carriers of rs1799963 compared with controls, and the difference remained unchanged after multivariate adjustment for potential confounders (Table 2). There was no interaction between smoking habits and thrombophilic polymorphisms in relation to IS at large (data not shown).

3.2. Distribution of the rs6025 and rs1799963 polymorphisms according to IS subtypes

Among the 423 stroke survivors, 70 (16.5%) experienced a stroke due to large artery atherosclerosis, 114 (27%) due to cardio-aortic embolism, 49 (11.6%) due to small artery occlusion, in 152 (36%), the etiology remained undetermined. Twenty two (5.2%) brain

Table 1
Characteristics of stroke survivors and controls.

	Stroke survivors n = 423	Controls n = 614	P Value
Age, years	66.34 ± 10.42	60.99 ± 6.65	<0.001
Gender (male), n (%)	257 (60.8)	303 (49.3)	<0.001
Current or past smoker, n (%)	251 (60.4)	312 (52.6)	0.001*
Increased alcohol intake, n (%)	87 (20.3)	145 (22.1)	0.08*
Education			
Basic, n (%)	238 (56.1)	254 (41.7)	<0.001*
Secondary, n (%)	127 (29.7)	259 (42.0)	
University, n (%)	57 (14.2)	99 (16.3)	
Body mass index, kg/m^2	28.9 [25.8–32.2]	27.9 [24.7–31.0]	0.013*
Hypertension, n (%)	388 (87.0)	379 (58.1)	<0.001*
Hyperlipidemia, n (%)	396 (92.6)	531 (85.9)	0.002*
Diabetes, n (%)	139 (30.1)	66 (10.2)	<0.001*
Elevated albuminuria, n (%)	90 (20.9)	20 (3.1)	<0.001*
Chronic kidney disease, n (%)	94 (18.9)	29 (3.6)	<0.001*

Mean ± SD and number are presented for age and gender, respectively.
Number and age- and gender-adjusted percentages are presented for categorical variables.
Age- and gender-adjusted median and interquartile range are presented for body mass index.
*P value obtained using age- and gender-adjusted logistic regression.

Table 2
Age- and gender-adjusted distribution of rs6025 and rs1799963 polymorphisms.

	Stroke survivors n = 423	Controls n = 614	Age- and gender-adjusted		Multivariate adjusted	
			OR (95% CI)	P value*	OR (95% CI)	P value*
rs6025, n (%)	44 (10.9)	53 (8.0)	1.23 (0.79–1.91)	0.37	1.22 (0.74–2.00)	0.43
rs1799963, n (%)	22 (5.3)	15 (2.4)	2.23 (1.08–4.58)	0.029	2.29 (1.04–5.02)	0.039

*P value obtained using logistic regression.
Adjusted for age, gender, body mass index, current or past smoking, hypertension, hyperlipidemia, diabetes, chronic kidney disease, elevated albuminuria, and education.

infarctions of other determined etiology and 16 (3.7%) of concomitant etiologies were excluded from the subtype analyses due to the small sample size and within-category pathogenic heterogeneity.

The clinical and genetic characteristics of stroke subtypes and controls are presented in Table 3. Among stroke subtypes, rs6025 was evenly distributed, though the opposite was observed in the distribution of rs1799963. The age- and gender-adjusted prevalence of rs1799963 was 10.3% among survivors of undetermined stroke, and this was approximately four times higher compared with controls. The distribution of rs1799963 in the remaining stroke subtypes did not contrast with control individuals.

The strong association between rs1799963 and undetermined stroke, independent of potential confounders, was confirmed by multinomial logistic regression using control individuals as a reference category (Table 4).

3.3. Interaction between the rs1799963 polymorphism and smoking

We observed a strong interaction between carriage of at least one copy of the rs1799963A allele and smoking associated with undetermined stroke (OR: 5.14; 95% CI: 1.65–16.01; p = 0.005), independent of age (OR: 1.14; 95% CI: 1.10–1.18; p < 0.001), hypertension (OR: 5.56; 95% CI: 2.68–11.54; p < 0.001), elevated albuminuria (OR: 4.83; 95% CI: 2.35–9.96; p < 0.001), smoking status per se (OR: 1.77; 95% CI: 1.13–2.77; p = 0.013), basic (OR: 1.93; 95% CI: 0.97–3.82; p = 0.061) and secondary education (OR: 1.18; 95% CI: 0.58–2.42; p = 0.654). The prevalence of rs1799963 in non-smokers was 2.3% in controls (7/302) and 3.9% in undetermined strokes (3/61), while 2.4% in controls (8/312) and 13.8% (12/91) in undetermined strokes among smokers. The step-wise adjusted OR of undetermined stroke according to smoking status and carriage of the rs1799963 polymorphism, using non-smokers non-carriers as reference category, is presented in Fig. 1.

4. Discussion

In this analysis, we evaluated differences in the distribution of the rs6025 and rs1799963 polymorphisms among hospital-based IS survivors by stroke subtypes compared with population-based controls. We demonstrated that the modest association of rs1799963 with IS at large is subject to the strong and exclusive association with its undetermined subtype, confined largely to smokers. Interestingly, the odds ratio of brain ischemia gradually increased with narrowing down the stroke survivors to those of undetermined cause and subsequently to smokers. On the contrary, there was no association between rs6025 and IS in general, or any subtype.

In the present analysis, the frequency of rs1799963 in healthy controls is comparable with that of blood donors from the Central Bohemia Region [20]. As the population-based controls were from the same geographical area as the cases, selection bias is limited.

Table 3
Demographic, clinical and genetic characteristics of ischemic stroke subtypes and controls.

	LAA n = 70	CAE n = 114	Lacunar n = 49	Undetermined n = 152	Controls n = 614	P Value
Age	64.50 ± 9.06	68.18 ± 10.91†	67.27 ± 9.4	67.91 ± 8.53†	60.99 ± 6.65$^{\dagger\ddagger\$\Delta}$	<0.001
Gender (male), n (%)	58 (82.9)	58 (50.9)‡	31 (63.3)	88 (57.9)‡	303 (49.3)‡	<0.001
Current or past smoker, n (%)	54 (78.1)	52 (45.5)†	29 (61.9)	91 (60.8)	312 (52.8)†	0.001*
Increased alcohol intake, n (%)	23 (30.2)	21 (19.2)	10 (21.4)	26 (18.3)	145 (22.1)	0.113*
Education						
Basic, n (%)	46 (64.1)	58 (52.5)	26 (57.1)	88 (57.3)	254 (41.7)$^{\Delta}$	<0.001*
Secondary, n (%)	16 (20.3)	36 (30.3)	19 (35.7)	47 (31.5)	259 (41.9)‡	
University, n (%)	8 (15.6)	20 (17.2)	4 (7.1)	16 (11.3)	99 (16.4)	
Body mass index, kg/m^2	29.0 [24.9–31.8]	28.4 [25.1–33.6]	29.7 [26.5–32.5]	29.4[26.5–32.1]	27.9 [24.7–31.0]	0.007*
Hypertension, n (%)	64 (84.1)	109 (91.0)	47 (95.2)	143 (92.9)	379 (57.8)$^{\dagger\ddagger\$\Delta}$	<0.001*
Hyperlipidemia, n (%)	69 (96.9)	103 (86.9)	46 (95.2)	141 (92.9)	531 (85.9)	0.025*
Diabetes, n (%)	19 (25.0)	38 (30.0)	24 (50.0)	47 (29.4)	66 (10.1)$^{\dagger\ddagger\$\Delta}$	<0.001*
Elevated albuminuria, n (%)	14 (20.6)	33 (26.3)	9 (20.5)	28 (18.9)	20 (3.0)$^{\dagger\ddagger\$\Delta}$	<0.001*
Chronic kidney disease, n (%)	14 (17.2)	30 (22.2)	12 (21.4)	32 (19.2)	29 (3.6)$^{\dagger\ddagger\$\Delta}$	<0.001*
rs6025, n (%)	6 (7.8)	14 (12.1)	5 (11.9)	14 (8.8)	53 (8.1)	0.667*
rs1799963, n (%)	1 (3.1)	3 (2.0)	1 (2.4)	15 (10.3)	15 (2.4)$^{\Delta}$	0.001*

Mean ± SD and number are presented for age and gender, respectively.
Number and age- and gender-adjusted percentages are presented for categorical variables.
Age- and gender-adjusted median and interquartile range are presented for body mass index.
LAA - large artery atherosclerosis; CAE - cardio-aortic embolism.
*P value obtained using an age- and gender-adjusted generalized linear model.
†P < 0.05 vs. LAA.
‡P < 0.05 vs. CAE.
$^{\$}$P < 0.05 vs. lacunar.
$^{\Delta}$P < 0.05 vs. undetermined.
$^{\dagger\ddagger\$\Delta}$P values corrected for multiple comparisons.

Table 4
Multivariate multinomial regression analysis of ischemic stroke subtypes with controls as reference category.

	LAA		CAE		Lacunar		Undetermined	
	OR (95% CI)	P Value	OR (95% CI)	P Value	OR (95% CI)	P Value	OR (95% CI)	P Value
rs1799963	0.53 (0.06–4.40)	0.552	1.22 (0.32–4.66)	0.774	0.90 (0.11–7.38)	0.920	3.67 (1.52–8.87)	0.004
Age	1.05 (1.00–1.09)	0.015	1.09 (1.06–1.13)	<0.001	1.08 (1.03–1.13)	0.001	1.10 (1.07–1.13)	<0.001
Gender (male)	4.00 (2.00–8.04)	<0.001	1.08 (0.66–1.77)	0.746	1.56 (0.78–3.13)	0.207	1.29 (0.84–1.99)	0.247
Current or past smoker	2.75 (1.44–5.24)	0.002	1.09 (0.67–1.78)	0.722	1.56 (0.79–3.10)	0.202	1.70 (1.10–2.63)	0.017
Education†								
Basic	1.95 (0.84–4.52)	0.120	0.81 (0.43–1.55)	0.529	1.86 (0.60–5.80)	0.282	1.83 (0.95–3.54)	0.072
Secondary	0.77 (0.30–1.95)	0.578	0.59 (0.30–1.17)	0.130	1.65 (0.52–5.24)	0.396	1.09 (0.55–2.16)	0.816
Hypertension	3.74 (1.52–9.21)	0.004	6.27 (2.43–16.18)	<0.001	6.19 (1.43–26.72)	0.015	4.57 (2.22–9.44)	<0.001
Hyperlipidemia	9.19 (1.22–69.17)	0.031	1.00 (0.46–2.15)	0.999	1.44 (0.41–5.03)	0.566	1.77 (0.81–3.86)	0.153
Diabetes	1.47 (0.77–2.80)	0.247	1.74 (1.01–3.00)	0.047	3.80 (1.91–7.58)	<0.001	1.55 (0.94–2.57)	0.089
Elevated albuminuria	2.84 (1.27–6.39)	0.011	6.55 (3.30–13.00)	<0.001	2.54 (0.99–6.52)	0.053	3.53 (1.78–7.00)	<0.001
Chronic kidney disease	4.22 (1.81–9.81)	0.001	2.52 (1.29–4.95)	0.007	3.07 (1.27–7.42)	0.013	2.01 (1.04–3.86)	0.037

LAA – large artery atherosclerosis; CAE – cardio-aortic embolism.
†University as reference category.

Even though the prevalence of rs1799963 among IS survivors is low (5.6%), it is significantly higher than in the general population without any documented cardiovascular disease (2.6%). Yet, rs1799963 was found in 10.3% of undetermined strokes, and in 13.8% of undetermined strokes among smokers. For comparison, the prevalence of rs1799963 among patients with a history of deep vein thrombosis ranges between 6.2 and 8%, which is more than two to three times higher than in the general European population (0.7–4.0%) [24–26].

Ischemic stroke is a heterogeneous disease, thus studies lacking stroke subtyping are prone to be unsuccessful in detecting any association. The validated Causative Classification of Stroke System was developed in order to identify the most likely mechanism in the case of multiple competing causes [6]. Despite diagnostic efforts, the etiology of IS remains undetermined in around 30–40% of patients. This has an unfavorable impact on their prognosis in terms of a high recurrence rate (14–30%), increased disability, and impaired survival [27,28]. However, the only prospective study comparing stroke patients with and without thrombophilia does not indicate that carriage of the polymorphism could account for an increased recurrence rate of stroke [29]. In contrast, some studies have indicated that rs6025 might be a protective factor against IS in the elderly; however, this does not seem biologically plausible [30]. Instead, carriage of rs6025 might protect from hemorrhagic transformation of ischemic brain tissue [31]. In our study, patients who deceased during hospitalization for the index event or during the period between their discharge and examination were not tested for thrombophilic polymorphisms, therefore their prognostic significance could not be evaluated. It is also uncertain whether any secondary preventive measures are needed. Prospective studies evaluating anticoagulation treatment among carriers of thrombophilic genotype with brain infarction are lacking, and recommendations for further management of these patients are based on consensus of experts. In spite of lacking evidence, recent guidelines suggest considering long-term anticoagulation therapy in IS patients with hypercoagulable states, particularly in those with recurrent atherothrombotic events and venous thromboembolism [32].

The mechanism of IS in patients with hereditary thrombophilia remains uncertain. As PFO and deep venous thrombosis were more common in undetermined strokes, paradoxical embolism has been assumed. However, a recent meta-analysis of case–control studies did not provide evidence for an association between hereditary thrombophilia and PFO-related stroke [4]. A similar conclusion was drawn in a later study by Favaretto et al. Consistent with our findings, the prevalence of rs1799963, but not of rs6025, was significantly higher in patients with acute stroke of unknown cause compared with controls, and irrespective of PFO [9]. The lack of an association of stroke and rs6025, the strongest predictor of venous thromboembolism, is also supportive of a causal mechanism other than paradoxical embolism. Notably, rs6025 and rs1799963 polymorphisms may lead to a different manifestation of venous thromboembolism. Carriers of rs1799963 have an increased risk of isolated pulmonary embolism and more severe clinical manifestations than those with rs6025 [33].

In our study, the association between rs1799963 and

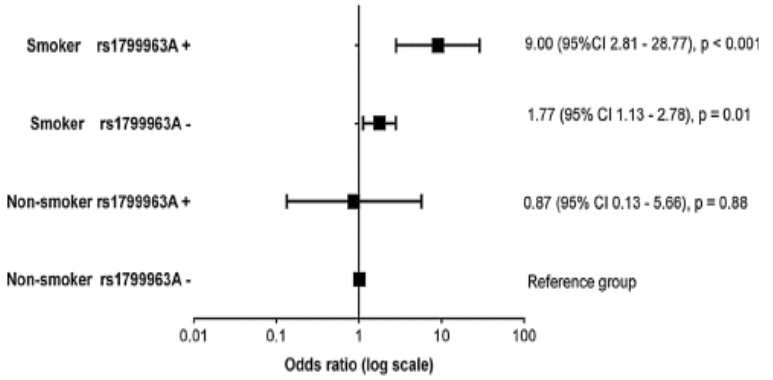

Fig. 1. Multivariate adjusted odds ratio of stroke of undetermined subtype according to smoking status and rs1799963.

undetermined stoke was strongly modified by tobacco smoking. Enhanced thrombosis appears to be a leading factor in the pathogenesis of acute cardiovascular events among smokers. The risk of stroke attributable to smoking declines after smoking cessation; however, it takes several years of abstinence to reduce the risk to the level of lifetime nonsmokers [34,35]. Thrombosis is a complex process which involves platelets, endothelial cells, sub-endothelial vascular tissues, coagulation cascade, and the fibrinolytic system. Smoking-enhanced thrombogenesis is the result of a variety of abnormalities such as accelerated turnover and activation of platelets, increased expression of tissue factor, increased circulating levels of fibrinogen, impaired thrombolysis, and endothelial injury [36]. It has been estimated that rs1799963 is associated with a mean 30% increase in plasma prothrombin level [24]. Although the case–control design of our study precludes inferences about causality, we assume that increased prothrombin level given by genetic predisposition may in combination with complex changes induced by smoking lead to an increased tendency for blood clotting and subsequently to IS.

Our findings are in line with previous studies documenting the gene–environment interaction between thrombophilic polymorphisms and established cardiovascular risk factors [37,38]. However, an interaction between rs1799963 and smoking in association with specific subtypes of IS has not been tested before. Pezzini et al. observed a gene-dose and a synergistic effect between thrombophilic polymorphisms and smoking in association with IS among adults younger than 45 years [39]. Our results extend the findings by Rosendaal et al., who reported a synergistic effect between cigarette smoking and Prothrombin G20210A (rs1799963) on the risk of myocardial infarction in young women [39]. In contrast, a similar study by Lalouschek et al. in adults younger than 60 years reported a highly increased risk of cerebral ischemia in women who carried Factor V Leiden (rs6025), and smoked. The prevalence of Prothrombin G20210A (rs1799963) was significantly higher in male patients compared with controls; however, no interaction with smoking was observed [40]. Although female sex hormones and use of oral contraception might affect the relationship between thrombophilic polymorphisms and ischemic cardiovascular events, no interaction with gender was found in our study (results not shown). While the lack of stroke subtyping might explain the discrepancy between these results, the underlying mechanism remains unresolved. It might be possible that the interaction with smoking modulates the association of both polymorphisms with cardiovascular diseases, though the effect might be population-specific. Furthermore, interaction with other cardiovascular risk factors, such as lipoprotein(a), which is known to reduce fibrinolysis, cannot be excluded [41].

It has been advocated that screening for inherited thrombophilia in IS patients is not justifiable [4]. However, this assumption is based on only a few negative case–controls studies [8–13]. The failure to detect an association could be explained by the lack of stroke subtyping, analyzing only particular subtypes, not including a population-based control group, and neglecting gene–environment interactions.

Some potential limitations of our analysis should be noted. Controls were significantly younger compared with cases (Table 1). Although all reported analyses are age-adjusted, a potential bias cannot be completely excluded. The reason for this discrepancy is that the controls (aged 50–75 years) were selected from a representative population random sample, whereas the cases (aged 18–80 years) are consecutive survivors of their first documented IS. Still, after excluding survivors older than 75 years, the findings remained unchanged, while the number of survivors decreased from 423 to 330 and the assumption of older controls was not accomplished (data not shown). Given these details, we assume that further exclusion of "older" stroke survivors would not substantially change the reported findings, while the power of the study would be considerably decreased. Furthermore, controls did not undertake exactly the same phenotyping protocol as cases, which may have led to underestimation of the presence of the disease in the control group. However, this should not underestimate the prevalence of genotypes in our control group, and thus false positive associations should be ruled out. A consistent evaluation of the venous system and transesophageal imaging of the left atrium were not performed in each patient. This could shed more light on the pathophysiology of stroke in the presence of hereditary thrombophilia. Although prothrombin levels were not assessed in this analysis, previous studies have convincingly documented that carriers of rs1799963 present with higher plasma prothrombin levels compared with non-carriers [24,42]. Another possible limitation is that the groups of patients by stroke subtypes were not equally represented and some subgroups were relatively small. Therefore, false negative results due to the error of small numbers cannot be ruled out. In total, only one stroke survivor with large artery atherosclerosis and lacunar stroke each carried a copy of the rs1799963A allele, which precludes interaction analysis in these subgroups. Conversely, except for undetermined stroke, the prevalence of the rs1799963A allele did not differ across the subgroups and was similar to that previously reported in the Central Bohemian Region [20]. Because of the large confidence intervals, the results of the interaction analysis require confirmation with a larger number of smoking subjects.

5. Conclusion

Even though rs1799963 plausibly accounts for only a negligible proportion of cerebral ischemic events, our results suggest that its role might be restricted to a specific subgroup of patients. In the present study of hospital-based consecutive survivors of the first IS and population-based controls, rs1799963 was exclusively associated with IS of undetermined subtype. Furthermore, there was strong evidence for synergistic interaction between rs1799963 and tobacco smoking. These findings extend our knowledge on the gene–environment interaction in IS and may help to identify subgroup of patients who may potentially benefit from the screening. However, the clinical impact of second-line screening for rs1799963 as well as optimal secondary prevention strategies need to be further evaluated in prospective studies. Still, we are convinced that carriers of rs1799963 who smoke should be informed about their increased risk of IS.

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Disclosures

The authors report no conflict of interest.

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Desphospho-uncarboxylated matrix Gla-protein is associated with mortality risk in patients with chronic stable vascular disease

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ABSTRACT

Background: Vitamin K is the essential co-factor for activation of matrix Gla-protein (MGP), the natural inhibitor of tissue calcification. Biologically inactive, desphospho-uncarboxylated MGP (dp-ucMGP) is a marker of vascular vitamin K status and is described to predict mortality in patients with heart failure and aortic stenosis. We hypothesized that increased dp-ucMGP might be associated with mortality risk in clinically stable patients with chronic vascular disease.

Materials and methods: We examined 799 patients (mean age 65.1 ± 9.3 years) who suffered from myocardial infarction, coronary revascularization or first ischemic stroke (pooled Czech samples of EUROASPIRE III and EUROASPIRE-stroke surveys), and followed them in a prospective cohort study. To estimate the 5-year all-cause and cardiovascular mortality we ascertained vital status and declared cause of death. Circulating dp-ucMGP and desphospho–carboxylated MGP (dp-cMGP) were measured by ELISA methods (IDS and VitaK).

Results: During a median follow-up of 2050 days (5.6 years) 159 patients died. In the fully adjusted multivariate Cox proportional hazard model, the patients in the highest quartile of dp-ucMGP (≥977 pmol/L) had higher risk of all-cause and cardiovascular 5-year mortality [HRR 1.89 (95% CI, 1.32–2.72) and 1.88 (95% CI, 1.22–2.90)], respectively. Corresponding HRR for dp-cMGP were 1.76 (95% CI, 1.18–2.61) and 1.79 (95% CI, 1.12–2.57).

Conclusions: In patients with overt vascular disease, circulating dp-ucMGP and dp-cMGP were independently associated with the risk of all-cause and cardiovascular mortality. Since published results are conflicting regarding the dp-cMGP, we propose only circulating dp-ucMGP as a potential biomarker for assessment of additive cardiovascular risk.

1. Introduction

Despite the therapeutic control of major conventional risk factors in secondary prevention of vascular complications [1], several other processes may also contribute to the complex pathogenesis of cardiovascular diseases. In recent years, close attention was paid to vascular calcification [2–4]. By studying the process of vascular calcification, we might find promising parameters for early detection of subclinical atherosclerosis and more accurate estimations of residual risk in patients with overt or preclinical cardiovascular disease (CVD).

One approach uses direct measurement of coronary artery calcification (CAC) [2]. For this purpose, electron-beam or multidetector computed tomography (EB-CT or MD-CT) is used and the scoring system for this purpose was developed (designated as CAC or Agatston score) [2]. A meta-analysis of four studies by Pletcher

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et al. [3] found a linear relationship between CAC and the risk of future vascular event; the relative risk ratio for subjects with intermediate degree of CAC (defined as CAC score 1–100) was 2.1, while in severely affected subjects (CAC score >400) the relative risk raised up to 10 [3]. Another meta-analysis summarizing six prospective trials on 27,622 asymptomatic subjects stated that the relative risk of death or myocardial infarction for subjects with any detectable CAC was 4.3 times higher when compared to subjects with CAC score of 0 [2]. Despite convincing evidence for CAC scoring in cardiovascular risk assessment, its practical application is limited. The EB-CT or MD-CT techniques are expensive and their cost-effectiveness, especially in low-risk populations, is questionable [2].

A different approach for estimating vascular calcification is the measurement of vascular calcification biomarkers [5,6]. Matrix Gla-protein (MGP) secreted primarily by chondrocytes and vascular smooth muscle cells in the arterial media [7,8] is a potent natural inhibitor of vascular calcification. MGP-deficient transgenic mice exhibit massive arterial calcification and die prematurely from vascular events [9]. Vitamin K plays a crucial role in synthesis of mature MGP [4]. Two forms of vitamin K are found in our diet: vitamin K_1 (phylloquinone, found in leafy green vegetables) and vitamin K_2 (menaquinones, found in cheese, meat, eggs, etc.). Vitamin K serves as co-factor for the enzyme γ-glutamate carboxylase that converts glutamate residues into γ-carboxyglutamate (Gla). These Gla-residues serve as calcium-binding groups, which are essential for the activity of all Gla-containing proteins including MGP. Besides carboxylation, MGP also undergoes posttranslational serine phosphorylation during maturation. Whereas carboxylation is essential for its calcification inhibitory activity, its cellular secretion is enhanced by phosphorylation [10,11]. Remarkably in the healthy population both carboxylation and phosphorylation are incomplete, so that different MGP isoforms are found in the circulation. The absence of calcium-binding groups in desphospho-uncarboxylated MGP causes the inability to interact with intravascular calcium deposits, which is why this isoform is readily set free in the circulation independent of the calcification degree of the tissue in which it was formed [10].

The present paper focuses on two isoforms of MGP: desphospho-uncarboxylated MGP (dp-ucMGP) and desphospho-carboxylated MGP (dp-cMGP). High circulating dp-ucMGP represents the fully inactive form. It reflects low dietary intake of vitamin K resulting in less efficient inhibition of vascular calcification [12]. Indeed the circulating dp-ucMGP was positively associated with CAC quantified by Agatston score and inversely related to vitamin K status [10,13]. Plasma dp-ucMGP was also reported to be independently associated with mortality in patients with symptomatic aortic stenosis [14] and heart failure [15], as well as in dialysis patients [16].

To our knowledge, no previous study investigated whether non-phosphorylated species of MGP (i.e. dp-ucMGP and dp-cMGP) correlate with CV mortality in patients with manifest vascular disease. We addressed this question in clinically stable patients with coronary heart disease or after stroke.

2. Methods

2.1. Study population

The study population consists of Czech patients examined in the framework of two well-defined surveys in patients with coronary heart disease (CHD, EUROASPIRE III) [17] or in patients after first ischemic stroke (EUROASPIRE III-stroke survey) [18] in 2006/2007, the selection and standard protocol of examination were in details described elsewhere [18]. Both surveys were conducted in the two centers in the Czech Republic: the University Hospital Pilsen and the Cardio-Centre of Institute of Clinical and Experimental Medicine in Prague. The study was carried out according to the guidelines for Good Clinical Practice. Local Ethical Committees approved of the study protocols. All of the participants gave written informed consent. The data were stored and evaluated under the provisions of the Czech data protection act.

CHD patients [17] aged ≤80 years hospitalized for any of following discharge diagnosis were retrospectively identified from hospital records: first coronary bypass graft (CABG), first percutaneous trans-luminal coronary angioplasty (PTCA) and acute myocardial infarction or ischemia. Recruitment of patients started with the most recent hospital record and proceeded backwards until the required sample of 600 subjects was achieved. The interview of patients was performed 6–36 months after the index event (coronary event or revascularization).

The stroke patients were selected in the same manner [18]. A total of 507 consecutive patients aged ≤80 years hospitalized for first ischemic stroke were selected and the responders were interviewed.

2.2. Clinical examinations and biochemical measurements

Information on personal and demographic characteristics, personal and family history of coronary heart disease, life-style and pharmacotherapy were obtained at the interview. The following clinical examinations were performed: height and weight were measured in light indoor clothes without shoes using SECA 220 scales and measuring sticks. Waist circumference was measured using a steel tape measure. Blood pressure (BP) was measured twice in the sitting position on the right arm using a standard mercury sphygmomanometer. Breath carbon monoxide was measured by a SMOKERLYSER device (model EC 50, Bedfont Scientific, U.K) to verify the reported smoking habit. Venous blood samples were drawn after at least 12 h of overnight fasting.

All laboratory examinations were performed in series from aliquots stored at −80° and included: estimation of serum total (TCHOL) and HDL (HDL) cholesterol, using an ARCHITECT c800 analyzer (Abbott Laboratories, Germany) and DOT Diagnostics commercial kits (Czech Republic); the same analyzer was used for measuring serum triglycerides (TG) and glucose (GLU), whereas brainnatriuretic peptide (BNP) was measured in EDTA plasma using the Abbott commercial kits.

Both, dp-ucMGP and dp-cMGP were quantified in citrate plasma samples by pre-commercial sandwich (dual-antibody) ELISA kits at VitaK (Maastricht University, The Netherlands).Dp-ucMGP was assessed using the inaKtiv MGP iSYS kit (IDS, Boldon, UK), which is a dual-antibody test based on the sandwich ELISA developed by VitaK, Maastricht University, The Netherlands. Circulating dp-cMGP levels were measured by a sandwich ELISA in which the first antibody was directed against the non-phosphorylated sequence 3–15 and the second antibody against the carboxylated sequence 35–53 in human MGP.

2.3. Data management

We ascertained the vital status of patients through May 31, 2012 using National mortality registry of Czech Institute for Medical Information and Statistics. We used death certificates to specify the cause of death. From the 834 CHD patients or stroke patients who underwent the initial interview, we excluded 35 subjects because of incomplete follow-up data or impossible MGP estimation from technical reasons (insufficient plasma volumes, high lipemic plasma etc.).

For statistical analyses, we used STATISTICA 8 and STATA/SE 8 software. Standard statistical methods were used, i.e. Mann–Whitney *U*, χ^2 test, multiple step-wise linear regression and Cox proportional hazard regression. Conventional risk factors were dichotomized by usual cut-off points (see relevant section of tables), both MGP isoforms by their quartiles as follows: <521, 521–692, 693–976 and ≥977 pmol/L for dp-ucMGP, and <1918, 1918–2349, 2350–3006 and ≥3007 pmol/L for dp-cMGP (lower limits of 4th quartiles were used as cut-off points).

3. Results

The baseline characteristics of 482 CHD patients and 317 stroke patients are given in Table 1. The stroke patients were significantly older and had higher heart rate, TCHOL, LDL and HDL cholesterol, dp-ucMGP and dp-cMGP concentrations than CHD patients, while BNP concentration and waist circumference were lower. Stroke patients were more frequently female and treated with angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers (ACEi/ARBs) than CHD patients, whereas frequency of manifest heart failure and treatment with betablockers and statins had the opposite direction. The median (interquartile range) of plasma dp-ucMGP and dp-cMGP was 859 (521–977) pmol/L and 2566 (1915–3010) pmol/L, respectively. During median follow-up of 2050 days (5.6 years), 159 patients deceased, and 107 of these fatal events were considered cardiovascular. The corresponding 5-year all-cause and cardiovascular mortality were 17.9% and 12.4%, respectively, with higher mortality rates in stroke patients (Table 1).

Table 1
Baseline characteristics of study sample [mean (standard deviation) or proportion].

	Pooled data	CHD patients	Stroke patients	*p*
N	799	482	317	–
Age (years)	65.1 (9.31)	62.6 (8.63)	69.0 (8.9)	<0.0001
Male gender (%)	71.1	78.6	59.6	<0.0001
Current smoking (%)	18.9	20.5	16.0	0.14
Clinically manifest heart failure (%)[a]	27.0	36.9	12.0	<0.0001
Body mass index (kg/m^2)	29.3 (4.78)	29.4 (4.62)	29.1 (5.0)	0.12
Waist circumference (cm)	101.4 (12.3)	102.3 (11.7)	100.2 (13.1)	0.008
Systolic blood pressure (mm Hg)	136.3 (17.8)	135.7 (16.9)	137.2 (19.0)	0.26
Diastolic blood pressure (mm Hg)	80.4 (10.1)	80.6 (9.83)	80.0 (10.5)	0.48
Heart rate (beats/minute)	67.9 (11.8)	65.6 (10.4)	71.1 (12.8)	<0.0001
Total cholesterol (mmol/L)	4.82 (1.27)	4.62 (1.37)	5.12 (1.13)	<0.0001
HDL-cholesterol (mmol/L)	1.23 (0.36)	1.12 (0.29)	1.39 (0.39)	<0.0001
LDL-cholesterol (mmol/L)	2.84 (0.97)	2.72 (0.93)	3.03 (0.99)	<0.0001
Triglycerides (mmol/L)	1.70 (1.63)	1.80 (2.00)	1.56 (0.76)	0.12
Fasting glycemia (mmol/L)	6.85 (2.55)	6.90 (2.51)	6.78 (2.61)	0.21
BNP (ng/L)	120.8 (192.9)	153.3 (221.9)	70.5 (120.6)	<0.0001
dp-ucMGP (pmol/L)	858.8 (611.3)	803.3 (560.4)	943.6 (673.6)	<0.0001
dp-cMGP (pmol/L)	2568 (941)	2431 (898)	2779 (965.7)	<0.0001
Tx/w betablockers (%)	71.0	88.8	43.9	<0.0001
Tx/w ACEi or ARBs (%)	81.9	73.9	100	<0.0001
Tx/w statins (%)	69.8	82.6	50.5	<0.0001
Tx/w antidiabetics (%)	21.9	21.4	22.7	0.65
Tx/w warfarin (%)	10.6	5.7	17.6	<0.0001
All-cause 5-year mortality (%)	17.9	12.7	25.9	<0.0001
Cardiovascular 5-year mortality (%)	12.4	8.9	17.7	<0.0001

CHD, coronary heart disease; HDL, high density lipoprotein; LDL, low density lipoprotein; ACEi, angiotensin-converting enzyme inhibitors; ARBs, angiotensin II receptor blockers; BNP, brain natriuretic peptide; Tx/w, treatment with …; *p* value for difference between CHD patients vs. stroke patients.

[a] Patients with NYHA II or higher, known systolic dysfunction [EF<40%], history of hospitalization for heart failure or chronic treatment with loop diuretics.

Table 2
Multivariate association between MGP's and conventional risk factors and warfarin treatment (multiple linear step-wise regression).

Dependent variable:	dp-ucMGP		dp-cMGP	
	β coeff (SE)	*p* value	*β* coeff (SE)	*p* value
Age	0.859 (0.031)	0.0066	0.100 (0.041)	0.015
Male gender	−0.094 (0.031)	0.0026	−0.068 (0.040)	0.089
Stroke as inclusion diagnosis[a]	–	–	0.198 (0.043)	<0.0001
Current smoking	−0.101 (0.037)	0.0009	–	–
Clinically manifest heart failure	0.054 (0.039)	0.088	0.168 (0.041)	<0.0001
Body mass index	–	–	−0.085 (0.063)	0.18
Waist circumference	0.111 (0.03)	0.0003	0.157 (0.062)	0.012
Mean arterial pressure	0.052 (0.038)	0.088	−0.068 (0.039)	0.081
Heart rate	0.058 (0.031)	0.058	–	–
BNP	0.186 (0.042)	<0.0001	0.126 (0.042)	0.0018
Tx/w warfarin	0.542 (0.031)	<0.0001	−0.074 (0.039)	0.063

Following variables were in addition initially included into the full model: HDL and LDL cholesterol, triglycerides, glycemia, treatment with antidiabetics, statins and ACEi or ARBs.

[a] Stroke vs. coronary heart disease.

In step-wise multiple regression analysis, we identified the following covariates as significant positive determinants of dp-ucMGP concentrations: age, clinically manifest heart failure or stroke as inclusion diagnosis, waist circumference, BNP, and warfarin treatment, while negative associations were found with male gender and current smoking (Table 2). Similarly, dp-cMGP positively associated with age, stroke as inclusion diagnosis, heart failure, waist circumference, and BNP.

Fig. 1 shows the Kaplan–Meier survival curves. Increased levels (4th quartiles) of both dp-ucMGP and dp-cMGP were associated with significantly poorer survival.

We further analyzed the all-cause or cardiovascular mortality predictors using a multivariable adjusted Cox model (Table 3). Model A included dp-ucMGP and model B included dp-cMGP, respectively. After adjustment for covariates, patients in the highest quartile of both dp-ucMGP and dp-cMGP (i.e. 977 and 3007 pmol/L, respectively), had an almost two-fold higher risk of 5-year all-cause or cardiovascular mortality. However, including both factors into the same model, only dp-ucMGP kept its statistically significant predictive power (HRR 1.90. 95% confidence interval 1.30–2.77; $p = 0.001$) – *data not shown in table section*. Including both MGP isoforms into the same model did not increase the standard error of means of the regression coefficients, so we can exclude the co-linearity effect.

To explore the influence of warfarin treatment – which prevents the activation of MGP on mortality prediction, we performed two sensitivity analyses. First, we excluded all subjects treated with warfarin. The HRRs for dp-ucMGP and dp-cMGP were 1.89 and 1.72, respectively. Second, we added warfarin into the mortality model (Table 3). The use of warfarin did not produce any further additive mortality risk (HRR 1.01) and also hazard ratios for other factors remained virtually the same. Thus, the sensitivity analyses were confirmatory to the main results. Therefore, we did not add this factor into the final model. For similar reasons, we also omitted the creatinine clearance. Only 2.3% of the subjects in our series showed a creatinine clearance (by Cockcroft–Gault formula) lower than 0.6 mL/s and of them, only one subject having a value lower than 0.3 mL/s. Patients with a low creatinine clearance showed substantially higher dp-ucMGP than those with normal renal functions (1602 vs. 852 pmol/L, respectively.). However, the predictive power of dp-ucMGP on mortality remained even if creatinine clearance was added into the model as confounder.

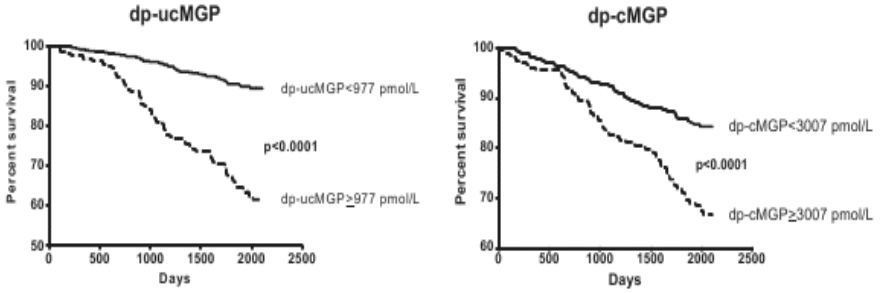

Fig. 1. Kaplan–Meier survival curves for all-cause mortality by dp-ucMGP and dp-cMGP subgroups (p value by Mantel–Cox test).

We further analyzed the adjusted mortality risk prediction of dp-ucMGP and dp-cMGP, when different cut-off points (based on MGP quartiles) were used. The first quartile was considered as the reference. We observed a trend for higher risk of 5-year total mortality in patients with dp-ucMGP concentrations higher than ≥521 or ≥693 pmol/L (i.e. lower limits of 2nd or 3rd quartiles). However, only in patients with the highest dp-ucMGP concentration (≥977 pmol/L) the result was significant (HR 2.01, 95% CI, 1.15–3.52; $p = 0.014$). The results for dp-cMGP were not statistically significant in the similar arrangement.

We also calculated the mortality risk prediction using 800 pmol/L as cut-off point (according to the manufacturer, an arbitrary upper limit of normal range of dp-ucMGP), but the corresponding HRR was nearly similar again [1.89 (95%CI 1.23–2.90) $p = 0.004$] – *data not shown in table section*.

Fig. 2 gives the age-adjusted 5-year all-cause mortality HRs for increased dp-ucMGP (panel A) and dp-cMGP (panel B) concentrations separately by pre-specified subgroups of its potential confounders (with respect to Table 2 results) or potent mortality predictors. In spite of the fact that elevated dp-ucMGP kept its predictive power in all subgroups, potential interactions were observed with age, current smoking and inclusion diagnosis (i.e. CHD vs. stroke). With regard to dp-cMGP we did not observe any potential interactions.

4. Discussion

The key finding of our study was that elevated dp-ucMGP concentrations were associated with higher cardiovascular and total mortality in stable patients with manifest vascular disease. Indeed, patients in the highest quartile of dp-ucMGP (≥977 pmol/L) had approximately 90% increase of 5-year all-cause or cardiovascular mortality risk (compared to those with lower concentrations) independently on conventional risk profile. Median concentration of dp-ucMGP in our sample of patients with manifest vascular disease was 2–3 times higher than in similarly aged subjects from the general population without prevalent cardiovascular disease (859 vs. 335 pmol/L) [5]. With respect to our findings and other reports we conclude that dp-ucMGP can be considered as a risk marker for cardiovascular disease.

To our knowledge, our study is the first one to examine the association between dp-ucMGP and mortality risk in patients with

Table 3
5-year total and cardiovascular mortality predictors in pooled sample of CHD and stroke patients (Cox proportional hazard model).

Independent variables	All-cause death HR (95% CI)	p value	Cardiovascular death HR (95% CI)	p value
Model A:				
Age	1.04 (1.02–1.07)	<0.0001	1.05 (1.03–1.08)	<0.0001
Male gender	1.30 (0.90–1.90)	0.33	1.33 (0.85–2.09)	0.21
Stroke as inclusion diagnosis[a]	2.80 (1.83–4.29)	<0.0001	2.66 (1.60–4.42)	<0.0001
Current smoking	1.21 (0.74–1.97)	0.09	1.12 (0.61–2.07)	0.72
Body mass index ≥ 30 kg/m^2	0.70 (0.49–0.99)	0.048	0.51 (0.33–0.80)	0.003
High blood pressure	0.69 (0.49–0.98)	0.035	0.64 (0.42–0.98)	0.037
LDL ≥ 2.5 mmol/L	0.81 (0.57–1.15)	0.24	0.81 (0.53–1.23)	0.32
Fasting glycemia ≥7 mmol/L	1.56 (1.09–2.22)	0.014	1.72 (1.13–2.62)	0.006
Treatment with statins	0.93 (0.63–1.38)	0.38	0.96 (0.60–1.53)	0.85
Brain natriuretic peptide ≥ 150 ng/L	3.64 (2.37–5.60)	<0.0001	1.75 (1.09–2.80)	0.02
Clinically manifest heart failure	1.82 (1.23–2.69)	0.003	3.91 (2.50–6.11)	<0.0001
dp-ucMGP ≥ 977 pmol/L[a]	1.89 (1.32–2.72)	0.001	1.88 (1.22–2.90)	0.004
Model B:				
Age	1.04 (1.02–1.07)	<0.0001	1.05 (1.03–1.08)	<0.0001
Male gender	1.27 (0.83–1.85)	0.21	1.31 (0.83–2.05)	0.24
Stroke as inclusion diagnosis[a]	2.99 (1.95–4.59)	<0.0001	2.79 (1.67–4.66)	<0.0001
Current smoking	1.06 (0.66–1.72)	0.81	0.97 (0.53–1.78)	0.92
Body mass index ≥ 30 kg/m^2	0.74 (0.52–1.05)	0.09	0.54 (0.34–0.84)	0.007
High blood pressure	0.71 (0.51–1.01)	0.052	0.66 (0.44–1.01)	0.055
LDL ≥ 2.5 mmol/L	0.86 (0.60–1.23)	0.41	0.87 (0.57–1.33)	0.51
Fasting glycemia ≥7 mmol/L	1.55 (1.09–2.21)	0.015	1.73 (1.13–2.63)	0.011
Treatment with statins	0.93 (0.63–1.36)	0.69	0.95 (0.60–1.52)	0.84
Brain natriuretic peptide ≥ 150 ng/L	3.70 (2.55–5.36)	<0.0001	4.28 (2.76–6.64)	<0.0001
Clinically manifest heart failure	1.89 (1.24–2.76)	0.002	1.73 (1.07–2.80)	0.026
dp-cMGP ≥ 3007 pmol/L[a]	1.76 (1.18–2.61)	0.024	1.79 (1.12–2.57)	0.016

[a] i.e. 4th quartile.

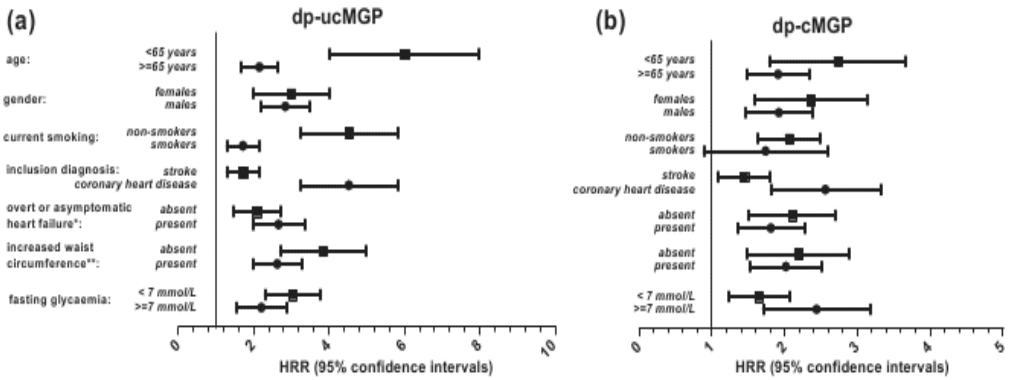

Fig. 2. Age-adjusted 5-year all-cause mortality hazard ratios for increased dp-ucMGP (panel A) and dp-cMGP (panel B) levels by subgroups of potential confounders. *BNP > 150 ng/L and/or patients with NYHA II or higher, known systolic dysfunction or history of hospitalization for heart failure; **waist circumference ≥102 cm in males or ≥88 cm in females.

manifest coronary heart disease or stroke. Our results are in line with the previous reports [5,19] in the general population [5] and in patients with chronic kidney disease (CKD) [19]. First, van den Heuvel et al. [5] reported that the highest tertile of dp-ucMGP (>400) was associated with a 2.7 times higher risk of cardiovascular event (fatal or non-fatal) in subjects from a general population subjects, who were free of CVD at baseline (thus subjects with gradually lower risk than our patients). The second study was performed in CKD patients [19]. This condition in its advanced stages is known to be complicated by soft-tissue calcification. In CKD subjects, dp-ucMGP was independently correlated with degree of aortic calcification (quantified by CT). Moreover, it also reflected the kidney disease progression (i.e. was inversely associated with glomerular filtration rate). Elevated dp-ucMGP (above median, i.e.>921) predicted all-cause mortality independently on age and disease stage but not from calcification score [19]. However, the association was lost after correction for confounders in Cox regression analysis.

A second important finding of our study is that dp-ucMGP might be a stronger predictor of mortality in patients with lower cardiovascular risk estimated by classical risk factors than in high risk patients. Indeed, more robust predictive power (3 times higher) of elevated dp-ucMGP was observed in patients with CHD compared to patients with stroke (Fig. 2). A similar pattern was observed by comparison between non-smokers and smokers, younger and older patients, euglycaemic and hypoglycemic patients. The only exception in this pattern was presence of heart failure. Elevated dp-ucMGP was associated with higher mortality risk in patients with overt (by medical history) or asymptomatic (using elevated BNP as a measure) heart failure. It is conceivable that the dp-ucMGP (or rather vascular calcification) might play a potential role in heart failure patients as additive risk factor. Ueland et al. [14] reported that patients with symptomatic aortic stenosis, who had an elevated dp-ucMGP (>950 pM) had higher mortality than those with lower concentrations of dp-ucMGP.

In our study, we also observed a positive association between a carboxylated isoform of MGP (i.e. dp-cMGP) and mortality risk. However, its predictive power disappeared when dp-ucMGP was added into the same model. To exert its anti-calcification activity, MGP should be carboxylated and therefore one would expect, that dp-cMGP would be inversely associated with vascular calcification and with mortality outcomes, while the opposite was found in our study. Available studies reported equivocal results. Dalmeijer et al. [13] reported positive association between circulating dp-cMGP and CAC (Agatston) score. Similarly, Ueland et al. [14] demonstrated that patients with calcific aortic valve stenosis showed higher circulating levels of dp-cMGP than healthy controls. Contrary to these [13,14] and our findings, Schlieper et al. [16] in study of 188 hemodialysis patients reported that low circulating dp-cMGP was associated with more than two-times higher mortality risk. These contradictory results may be explained by the fact that carboxylation not only precedes but also stimulates MGP phosphorylation. Since our tests only recognize desphospho-MGP isoforms, the phosphorylated fractions are not detected. As long as the factors regulating MGP phosphorylation remain unknown, dp-cMGP will remain an unpredictable marker in the diagnosis of cardiovascular disease. In view of this evidence we would presently not advocate the use of dp-cMGP as a biomarker of additive cardiovascular risk. Further research is necessary to elucidate the biological mechanisms of dp-cMGP in the pathophysiology of vascular/tissue calcification.

From a clinical point-of-view it is crucial, whether vascular calcification/CVD risk estimated by dp-ucMGP represents an irreversible process and end-stage "vascular disaster" or whether increased dp-ucMGP might be targeted by specific treatment. In several epidemiologic studies [20–22] it was shown, that vitamin K_2 intake (assessed by dietary questionnaires) was inversely associated with coronary calcification and incident cardiovascular morbidity. In a cross-sectional study among 564 post-menopausal women, subjects in highest quartile of vitamin K_2 intake had lower risk of coronary calcification [20]. In a prospective cohort study of 16,057 women, each incremental 10 μg K_2 dietary intake was associated with 9% reduction of CHD incidence [21]. Authors of another population-based cohort study [22] in 4807 subjects reported, that the highest tertile of vitamin K_2 dietary intake was associated with significantly lower risk of cardiovascular mortality and less severe aortic calcification (by 57% and 57%, resp.). Nonetheless, rather limited data are available from interventional studies. Six-week vitamin K_2 supplementation was followed by 17–46% decrease (by dose-dependent manner) of dp-ucMGP in hemodialysis patients [23] and supporting results were reported also in apparently healthy volunteers [24]. Recently, the data of a 3-year vitamin K_2 intervention study has become available, showing that vitamin K_2 supplementation is effective on decreasing arterial stiffening (Braam et al., unpublished results). Nonetheless, at this time there are no data showing that vitamin K supplementation may affect cardiovascular mortality. Moreover, ongoing trials are realized almost exclusively in the setting of advanced chronic kidney disease.

We might only speculate whether dp-ucMGP can serve as the biomarker of calcification and potentially replace the EB-CT/MB-CT techniques. It is obvious, that using the biomarker is far less

expensive and technically demanding (we are comparing simple laboratory estimation against rather expensive high-tech device) and thus, despite probably lower sensitivity, it could turn out to be more cost-effective. Currently, the clinical utility value of EB-CT or MD-CT is limited to a non-invasive scanning in asymptomatic subjects with intermediate cardiovascular risk, in whom the positive finding should lead to their re-classification into high-risk category and subsequent management [2]. The biomarker may potentially play the same role in the improvement of risk prediction, however, due to its assumed higher cost-effectiveness in much larger scale and perhaps also in subjects in low cardiovascular risk. Further studies comparing both methods are needed to definitively answer this question.

Our study has several limitations. First, the information about cause of death is based on ICD-10 codes declared in death certificates. Because several patients died at home, we were not able to ascertain every death cause. Therefore, the cardiovascular mortality rate (but not the all-cause mortality) may be biased (over rated?). Furthermore, we did not have information on non-fatal vascular events. Second, we have also no data available on vitamin D status, which is an important factor of calcium homeostasis and recognized cardiovascular risk factor [25]. It is generally assumed, that pathophysiological consequences of low D vitamin status also involves vascular calcification [26]. Moreover, several possible synergies between vitamin K and vitamin D metabolism were described regarding bone and tissue calcification. Namely, the promoter region for the MGP gene contains a 1,25-OH-D3 responsive element, regulating its transcription [27]. However, in the paper of van den Heuvel at al [5]. mortality risk was independent of 25-OH-D vitamin concentrations and therefore we may presume the same in our setting. Third, no data on nutritional intake of vitamin K were available. Vitamins K_1 and K_2 can be directly measured in the plasma, but their levels do not correlate with vitamin K-dependent functions. Osteocalcin ratio (OCR, a ratio between uncarboxyled and carboxyled osteocalcin) is frequently used as functional surrogate of vitamin K status. Dalmeijer et al. [13] found a strong correlation between OCR and dp-ucMGP circulating levels (indicating inverse relation between dp-ucMGP and vitamin K functional status) but not with nutritional intake of K vitamin (assessed by food questionnaire). Therefore, high dp-ucMGP value probably serves as better indicator of poor vitamin K status than data based on dietary-intake questionnaires. In our study, warfarin treated patients had significantly higher dp-ucMGP concentration than those not using warfarin (median concentration 1902 vs. 731 pmol/L). This finding reflects the suppressed vitamin K functional status in warfarin treated patients (a pharmacological mechanism of this drug).

On the other hand, our study has several strengths. Our well-defined study population was larger than other cohorts [5,13,14,16]. Moreover, we but not others [14,19] measured both desphospho-carbo and uncarboxylated MGP species.

5. Conclusions

In agreement with previous studies performed in the general population and in patients with chronic kidney disease, we confirmed in our sample of stable patients with overt cardiovascular disease that elevated dp-ucMGP is associated with a substantially higher mortality rate. Therefore, we propose that this factor may serve as a marker for estimation of CVD risk. Further research is needed to ascertain whether supplementation with vitamin K_2 – increasing rate of carboxylation of MGP and thus decreasing inactive dp-ucMGP levels–leads to the regression of vascular calcification and subsequently to lower mortality/morbidity risk.

Conflicts of interest

None.

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