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Review

Influence of Lipid Profiles on the Risk of Hemorrhagic Transformation after Ischemic Stroke: Systematic Review

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Key Words
Acute stroke · Cerebral ischemia · Cholesterol · Hemorrhagic transformation · Ischemic stroke · Lipoproteins · Triglycerides

Abstract
Background: It has been suggested that low cholesterol levels might be associated with an increased risk of hemorrhagic transformation (HT) in patients with acute cerebral ischemia. We systematically reviewed the literature to determine the influence of lipid profiles on the HT risk. ***Methods:*** We searched PubMed from 1966 and EMBASE from 1980 for studies that investigated the association between lipid profiles and HT. We performed a meta-analysis (weighted mean difference method) for the comparison between presence and absence of HT (all or symptomatic) for total, low-density-lipoprotein (LDL) and high-density-lipoprotein (HDL) cholesterol, and triglycerides. ***Results:*** Eight studies investigating 1,763 patients were eligible, but none was designed specifically to address this question. All studies recruited acute stroke patients selected on the presumed cause of cerebral ischemia or treatment received. The meta-analysis showed that: (i) patients with all HT had lower LDL cholesterol levels ($p = 0.008$) but no difference in HDL cholesterol levels ($p = 0.066$), total cholesterol ($p = 0.129$) and triglycerides ($p = 0.900$); (ii) patients with symptomatic HT had lower total cholesterol levels ($p = 0.035$) but did

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not differ in LDL (p = 0.056) and HDL cholesterol (p = 0.138) and triglyceride (p = 0.851) levels. ***Conclusion:*** HT is associated with baseline total and LDL cholesterol levels, but the mechanism of this association needs to be explored to identify preventive strategies.

Introduction

Hemorrhagic transformation (HT) of cerebral ischemia may occur either spontaneously or after treatment with recombinant tissue plasminogen activator (rt-PA) [1–3]. Although HT may sometimes be related to early recanalization and associated with better clinical outcomes [4], it is more often a predictor of worst clinical outcomes [2]. HT is favored by increasing age [2], stroke severity [5], blood pressure [6] and blood glucose level [7]. Identifying other factors predisposing to HT may lead to new preventive strategies. The risk of spontaneous intracerebral hemorrhage (ICH) increases with lower total cholesterol levels in humans [8] and animals [9], but not in patients treated with intensive lipid-lowering therapy after ischemic stroke [10].

We systematically reviewed published studies to determine the influence of lipid profiles on the risk of HT.

Methods

Literature Search Strategy

On March 2, 2011, we searched MEDLINE (http://www.ncbi.nlm.nih.gov/pubmed) from 1966 and EMBASE (http://ovidsp.ovid.com) from 1980 for studies that investigated the association between lipid profiles and HT in patients with acute cerebral ischemia. Because there is no medical subject heading (Mesh) term for HT, the search strategy in MEDLINE was based on the association of the following terms: ['Stroke' (Mesh) OR 'Cerebral Infarction' (Mesh) OR 'Infarction, Middle Cerebral Artery' (Mesh) OR 'Brain Ischemia' (Mesh) OR 'Intracranial Hemorrhages' (Mesh)] AND ['Lipids' (Mesh) OR 'Cholesterol' (Mesh) OR 'Cholesterol, HDL' (Mesh) OR 'Cholesterol, LDL' (Mesh) OR 'Triglycerides' (Mesh)]. In EMBASE, the search strategy was: stroke (exp) AND (lipid or cholesterol or HDL or high density lipoprotein or LDL or low density lipoprotein or triglycerides).

Studies missed by the electronic search have been identified from the authors' personal files and by hand searching the references cited in retrieved articles. We excluded abstracts of meetings and book chapters. We did not exclude any language. One reviewer (K.N.) performed the literature search and screened the titles and abstracts of retrieved citations to identify potentially suitable studies. The abstracts were read by 2 reviewers (K.N. and D.L.). Uncertainties and disagreements were resolved by consensus. The 2 reviewers extracted data from included studies.

Inclusion and Exclusion Criteria

Studies meeting the following criteria were included in the analysis: (i) adult patients with acute cerebral ischemia; (ii) a systematic search for HT in ischemic stroke patients; (iii) data on total cholesterol, and/or LDL and/or HDL cholesterol, and/or triglycerides, and (iv) a computed tomography (CT) or magnetic resonance imaging (MRI) scan of the brain for the assessment of HT. We excluded studies (i) published as reviews; (ii) including patients with intracranial hemorrhages of other origin than HT, and (iii) based only on autopsies.

Critical Appraisal

The external validity of the studies was defined as follows: level A for population-based studies recruiting consecutive patients; level B for hospital-based studies recruiting consecutive patients; level C for hospital-based studies recruiting a subgroup of consecutive patients encountered with a high frequency (e.g. treated by intravenous rt-PA and age >45 years), and level D for either nonconsecutive patients or patients from a rare subgroup (e.g. patients treated by intra-arterial recanalization).

Statistical Analysis

The first step consisted of reporting for each eligible study, the mean values (SD) of total, LDL and HDL cholesterol, and triglyceride levels separately for patients with and without all types of HT ($_{all}$HT), then separately for those with symptomatic HT ($_{s}$HT).

The second step consisted of a meta-analysis of eligible studies for the comparison between $_{all}$HT versus no HT, for total, LDL and HDL cholesterol, and triglyceride levels, then between $_{s}$HT and absence of $_{s}$HT for the same variables. We used the weighted mean difference (WMD) method. The research question for the meta-analysis was the influence of baseline levels of lipids on the risk of HT. The comparison was performed between HT and non-HT patients (then between $_{s}$HT and asymptomatic HT patients). The outcome was the baseline level of lipids (total, LDL and HDL cholesterol, and triglycerides evaluated separately). Statistical significance of the overall results was expressed with the p value in the test for overall effect, with $p < 0.05$ being considered as statistically significant. According to ranges for interpretation of I^2 following the *Cochrane Handbook for Systematic Reviews of Interventions* [11], I^2 values $\leq 40\%$ were considered as indicating homogeneity between studies. When I^2 was $\leq 40\%$ (p values are reported and $p > 0.05$ show evidence of no heterogeneity), we used a fixed model for meta-analysis. Statistics were performed with the STATA 11 software. The analysis was conducted according to the MOOSE consensus [12].

Results

The flow chart of the selection of studies is reported in figure 1. Eight studies gathering 1,763 patients were eligible [13–20].

Critical Appraisal

Most patients included in these studies were recruited between 2000 and 2007 [13–20]. All studies were published between 2007 and 2009 [13–20]. Of the 8 studies selected [13–20], 3 were from the same research group [13, 18, 19]. Two of them (including 168 patients) were not included in the meta-analysis because they did not provide comparisons between patients with and without HT. There might be a possible overlap between these 3 studies including 104, 142 and 26 patients, precluding all influence on the meta-analysis [13, 18, 19]. Only 1 study had a multicenter design [20], and none was international. None of these 8 studies was conducted in the setting of a clinical trial. Patients were consecutively recruited in 5 studies [13, 15–17, 20], not in 2 [18, 19], and the information was not reported in 1 [14]. Patients were, however, prospectively recruited in all studies [13–20]. The lipid profile was not determined specifically to address the question of the relationship with HT in 7 of the 8 studies [14–20]. Whether it was a prespecified question remains uncertain in 1 study [13]. Five were sponsored by public or institutional grants [13, 15, 16, 18, 19], and no detail on sponsoring was provided in 3 [14, 17, 20].

The characteristics of patients are detailed in table 1.

In 4 studies, patients were in the fasting state [13, 18–20]. Previous hypercholesterolemia was reported in 6 studies [14–16, 18–20], and ongoing statin therapy in all but 1 study [17].

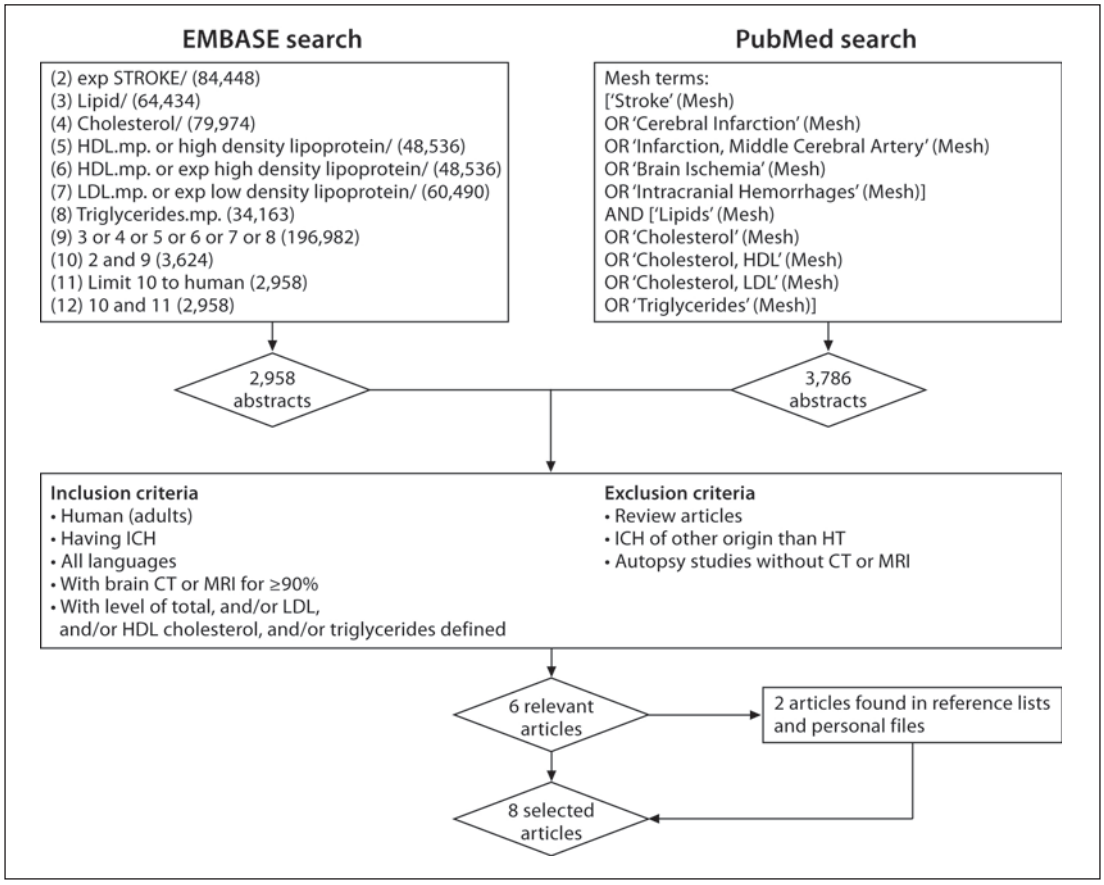

Fig. 1. Flow chart of the selection of articles.

No information about ongoing fibrate therapy or diet before stroke onset was available in any study. The method used to analyze lipids was detailed in 1 study [15]. All studies reported detailed results for LDL cholesterol levels [13–20], 7 for total cholesterol [13–19], 6 for HDL cholesterol [13–17, 19] and 5 for triglycerides [13–17].

The methods used to assess HT are detailed in table 2, and associated risk factors for HT are detailed in table 3. The methods used for analysis in each individual study are detailed in table 4.

Statistical Analysis of the Results of Included Studies

Individual Studies. The comparison of lipid profiles was possible in 2 studies [16, 17] for $_{all}$HT versus no HT, and in 4 for $_{s}$HT versus no $_{s}$HT [13–15, 17] (table 5).

Meta-Analysis. The meta-analysis of comparisons of lipid profiles in patients with and without $_{all}$HT included 2 studies [16, 17] gathering 688 patients. Detailed results are presented in figure 2 and table 5. LDL cholesterol levels were significantly lower in patients with $_{all}$HT ($p = 0.008$), but not total cholesterol ($p = 0.129$), HDL cholesterol ($p = 0.066$) and triglycerides ($p = 0.900$).

The meta-analysis of lipid levels in patients with and without $_{s}$HT included 4 studies [13–15, 17]. These 4 studies included 727 patients [13–15, 17]. One study [14] provided only mean values and no standard deviation. We used for this meta-analysis the standard deviation found in the study with the closest number of patients [13]. The detailed results are pre-

Table 1. Study population

	Bang et al. [13] 2007 (n = 104)	Montaner [14] 2008 (n = 60)[a]	Uyttenboogaart et al. [15] 2008 (n = 252)[b]	Kim et al. [16] 2009 (n = 377)	Meier et al. [17] 2009 (n = 311)	Restrepo et al. [18] 2009 (n = 142)	Bang et al. [19] 2009 (n = 26)[c]	Paciaroni et al. [20] 2009 (n = 491)[d]
Participants	AIS treated by IVT or IAT and/or angioplasty	AIS treated by IVT	AIS treated by IVT	Ath. and CE AIS	AIS treated by IAT or angioplasty	AIS treated by IAT or angioplasty	AIS with abnormal BBB permeability on 1st MRI	Ath. and CE AIS
External validity	C	C	C	C	D	D	D	C
Time from onset to admission	<3 h (IVT), <8 h (angioplasty)	<3 h	<4.5 h	≤7 days	<6 h (anterior stroke), <12 h (posterior stroke)	<12 h	<24 h	<12 h
Time of blood sampling reported	next morning	admission	admission	admission	admission	next morning	?	next morning
TIA excluded	+	+	+	+	+	+	+	+
Recurrent stroke excluded	–	–	–	–	–	–	–	–
Mean age, years	70.5	?	68	66	63	69	?	?
Male gender, %	49	?	54	62	57	51	?	?
Healthy controls	–	–	–	–	–	–	–	–
Controls without HT	+	+	+	+	+	+	+	+

+ = Characteristic fulfilled; – = characteristic not fulfilled; ? = unknown; AIS = acute ischemic stroke; Ath. = atherosclerotic; CE = cardioembolic; IVT = intravenous thrombolytic therapy; IAT = intra-arterial thrombolytic therapy; TIA = transient ischemic attack; BBB = blood-brain barrier. External validity was determined as follows: level A for population-based studies recruiting consecutive ischemic stroke patients; level B for hospital-based studies recruiting consecutive ischemic stroke patients; level C for hospital-based studies recruiting a subgroup of consecutive ischemic stroke patients considered by the investigator as encountered with a high frequency in practice (e.g. patients treated with IV t-PA or patients >45 years), and level D for either nonconsecutive patients or patients from a subgroup considered by the investigator as infrequent in practice (e.g. patients treated by intra-arterial recanalization or patients <45 years).

[a] Among 145 patients, 60 were evaluated for the association between HT and lipid profile.
[b] Among 301 patients, 252 were evaluated for the association between HT and lipid profile.
[c] Among 127 patients, 26 were evaluated for the association between HT and lipid profile.
[d] Among 1,125 patients, 491 were evaluated for the association between HT and lipid profile.

sented in figure 3 and table 5. Total cholesterol levels were significantly lower in patients with $_{s}$HT (p = 0.035), while LDL (p = 0.056) and HDL cholesterol (p = 0.138), and triglyceride levels did not differ (p = 0.851).

Discussion

This meta-analysis suggested that lower LDL cholesterol levels are associated with $_{all}$HT, while lower total cholesterol levels are associated with $_{s}$HT, and HDL cholesterol and triglycerides are not associated with the HT risk.

Methodology of Selected Studies

None of the 8 studies meeting the selection criteria [13–15, 17] was primarily designed to evaluate lipid profiles in HT explaining missing data, and there was heterogeneity for the assessment of HT. Most predictors of HT were taken into account except for silent vascular brain lesions, but a multivariate analysis including these predictors was available in only half of the studies. The external validity of the study population is therefore poor.

The method used to analyze serum lipids was usually not detailed, and the delay between stroke onset and sample collection ranged from admission to the next morning or 7 days. A previous study suggested changes in cholesterol levels at the acute stage of stroke [21],

Table 2. HT assessment

	Bang et al. [13] 2007 (n = 104)	Montaner [14] 2008 (n = 60)[a]	Uyttenboogaart et al. [15] 2008 (n = 252)[b]	Kim et al. [16] 2009 (n = 377)	Meier et al. [17] 2009 (n = 311)	Restrepo et al. [18] 2009 (n = 142)	Bang et al. [19] 2009 (n = 26)[c]	Paciaroni et al. [20] 2009 (n = 491)[d]
Admission imaging showing no bleeding	+	+	+	+	+	+	+	+
Assessed by CT	+	?	+	–	+	+	+	+
Assessed by MRI	+	?	–	+	+	+	+	–
Delay between stroke onset and assessment of HT	24–120 h or worsening	?	in case of worsening	<168 h	24 h or worsening	immediately after treatment	24 h or worsening	72–168 h
Inter- and intra-observer agreement evaluated	–	–	–	–	–	–	–	+
Follow-up >95% complete until the date of assessment of HT	+	+	?	+	+	+	+	+
Clear definition for HT	+	–	+[2]	+[3]	+[4]	+[5]	+[6]	+[7]
Clear definition for $_{s}$HT	+[1]	–	+[2]	–	+[4]	+[5]	–	+[7]
HT proven to occur in the same area as the ischemic event	–	–	–	–	–	–	+	+

+ = Characteristics fulfilled; – = characteristics not fulfilled; ? = unknown.

[a] Among 145 patients, 60 were evaluated for the association between HT and lipid profile.

[b] Among 301 patients, 252 were evaluated for the association between HT and lipid profile.

[c] Among 127 patients, 26 were evaluated for the association between HT and lipid profile.

[d] Among 1,125 patients, 491 were evaluated for the association between HT and lipid profile.

[1] Radiologically subcategorized as petechial HT or hematoma. Clinical categories for HT defined as asymptomatic HT (i.e. no clinical worsening on NIHSS); minor symptomatic HT (1- to 3-point increase in NIHSS score); major symptomatic HT (4-point increase in NIHSS score or 1-point deterioration in level of consciousness, and any symptomatic HT (any clinical worsening associated with HT, either major or minor).

[2] $_{s}$HT defined as a neurological deterioration within 48 h following rt-PA therapy with hematoma on CT scan.

[3] HT defined as absent or present on MRI.

[4] HT classified as symptomatic if parenchymal hematoma (PH) type 2 (PH-2) according to ECASS-II accompanied by an increase ≥4 points in NIHSS score or leading to death (SIST-MOST).

[5] $_{s}$HT defined as any acute intraparenchymal bleeding associated with worsening ≥4 points compared to the baseline NIHSS score.

[6] HT was radiologically defined and classified into 5 subtypes modified from Berger et al. [28]: hemorrhagic infarct (HI) type 1 (HI-1); small petechiae along the margins of the infarct; HI type 2 (HI-2); more confluent petechiae within the infarcted area but without space-occupying effect; PH type 1 (PH-1), defined as a hematoma in <30% of the infarcted area with some space-occupying effect; PH-2, hematoma in >30% or the infarcted area with substantial space-occupying effect, and subarachnoid hemorrhage. Patients could have >1 hemorrhage type.

[7] HT defined as any degree of hyperdensity within the area of low attenuation, and categorized as HI or PH. HI was defined as small petechiae along the margins of the infarct (HI-1) or as more confluent petechiae within the infarcted area but without space-occupying effect (HI-2). PH was defined as hematoma in 30% of the infarcted area with some slight space-occupying effect (PH-1) or as dense hematoma of ≥30% of the infarcted area with substantial space-occupying effect or as any hemorrhagic lesion outside the infarcted area (PH-2). In case of >1 hemorrhagic lesion on CT examination, the worst possible HT category was assumed. For analysis purposes, the authors considered HI-1 and HI-2 together and PH-1 and PH-2 together. HT was considered symptomatic if it was not seen on a previous CT and there was subsequently either a suspicion of hemorrhage or a decline in the neurological status.

but as this change is minimal [22], this has probably not had any influence on the results. Information on ongoing statin and fibrate therapy, and diet was not available in any study. This may have influenced the results, as statins and potentially fibrates may be associated with a better outcome in ischemic stroke [23, 24].

Relationship between Lipid Profiles and HT

It was not possible to analyze separately patients with and without reperfusion therapy, and according to the type of reperfusion therapy, because individual data were not available, and this would have led to subgroup analyses with a poor statistical power.

The meta-analysis showed a significant association between a low LDL cholesterol level and the presence of $_{all}$HT, and between a low total cholesterol level and the presence of $_{s}$HT. These results are important, because 1 of the 2 individual studies included in the meta-analysis for $_{all}$HT showed a nonsignificant tendency [17] and the other [16] was marginally sig-

Table 3. Description of predictors of HT

	Bang et al. [13] 2007 (n = 104)	Montaner [14] 2008 (n = 60)[a]	Uyttenboogaart et al. [15] 2008 (n = 252)[b]	Kim et al. [16] 2009 (n = 377)	Meier et al. [17] 2009 (n = 311)	Restrepo et al. [18] 2009 (n = 142)	Bang et al. [19] 2009 (n = 26)[c]	Paciaroni et al. [20] 2009 (n = 491)[d]
Ongoing anticoagulation at stroke onset reported	+	–	–	+	+	+	+	+
Ongoing antiplatelet therapy at stroke onset reported	+	+	+	+	+	+	+	+
Acute treatment with intravenous rt-PA reported	+	+	+	+	+	+	+	+
Acute treatment with intra-arterial thrombolytic therapy reported	+	–	–	–	+	+	+	–
Acute treatment with intra-arterial mechanical device reported	+	–	–	–	+	+	+	–
Anticoagulant therapy received before assessment of HT reported	?	?	?	?	–	?	?	+
Treatment with antiplatelet therapy received before assessment of HT	?	?	?	?	+	?	?	+
Prior arterial hypertension reported	+	+	+	+	+	+	+	+
Admission blood glucose level provided	+	–	+	+	–	+	+	+
Admission blood pressure provided	+	–	+	+	–	+	+	+
Admission NIHSS score provided	+	+	+	+	+	+	+	+
Presumed causes detailed	+	+	–	+	+	+	–	+
Location of cerebral infarct detailed	–	+	–	+	+	+	+	+
Infarct volume reported on DWI	–	?	NA	–	–	–	+	NA
ASPECT score reported	–	?	–	–	–	–	–	–
Presence of leukoaraiosis reported	–	–	–	+	–	–	–	–
Presence of silent infarcts reported	–	–	–	–	–	–	–	–
Presence of microbleeds reported	–	–	–	+	–	–	–	–
Previous symptomatic stroke lesion reported	–	–	–	+	–	–	–	–

+ = Characteristics fulfilled; – = characteristics not fulfilled; ? = unknown; NA = not applicable; DWI = diffusion-weighted imaging; ASPECT = Alberta Stroke Program Early CT Score.

[a] Among 145 patients, 60 were evaluated for the association between HT and lipid profile.

[b] Among 301 patients, 252 were evaluated for the association between HT and lipid profile.

[c] Among 127 patients, 26 were evaluated for the association between HT and lipid profile.

[d] Among 1,125 patients, 491 were evaluated for the association between HT and lipid profile.

nificant. The influence of HDL cholesterol seems more disputable because none of the studies has shown any significant result for both $_{all}$HT and $_{s}$HT, and the meta-analyses provided nonsignificant results in opposite directions. There is no statistical association between baseline triglycerides and risk of both $_{all}$HT and $_{s}$HT, although 1 individual study [15] suggested higher triglyceride levels in $_{s}$HT.

Therefore, the association between lipid profile and risk of HT is likely to be mediated by LDL cholesterol. This result is important because LDL cholesterol may be influenced by statins. The question of whether rt-PA is safe in patients with low LDL cholesterol levels or on statin treatment is therefore important: although patients treated with statins have less severe cerebral infarcts [25], a large European multicenter study showed that this effect is lost in patients treated concomitantly with rt-PA [26]. The underlying mechanism of increased HT with low levels of LDL cholesterol is not established. Cholesterol may be important for the integrity of small vessels [8] and of the neurovascular unit.

Although the mechanisms of HT and spontaneous ICH are different, it should be emphasized that the results of this meta-analysis mirror the findings of the INTERSTROKE [27] study showing a link between low LDL cholesterol and the risk of spontaneous ICH but not with those of SPARCL showing no relation between a low LDL cholesterol level and the risk of ICH [10].

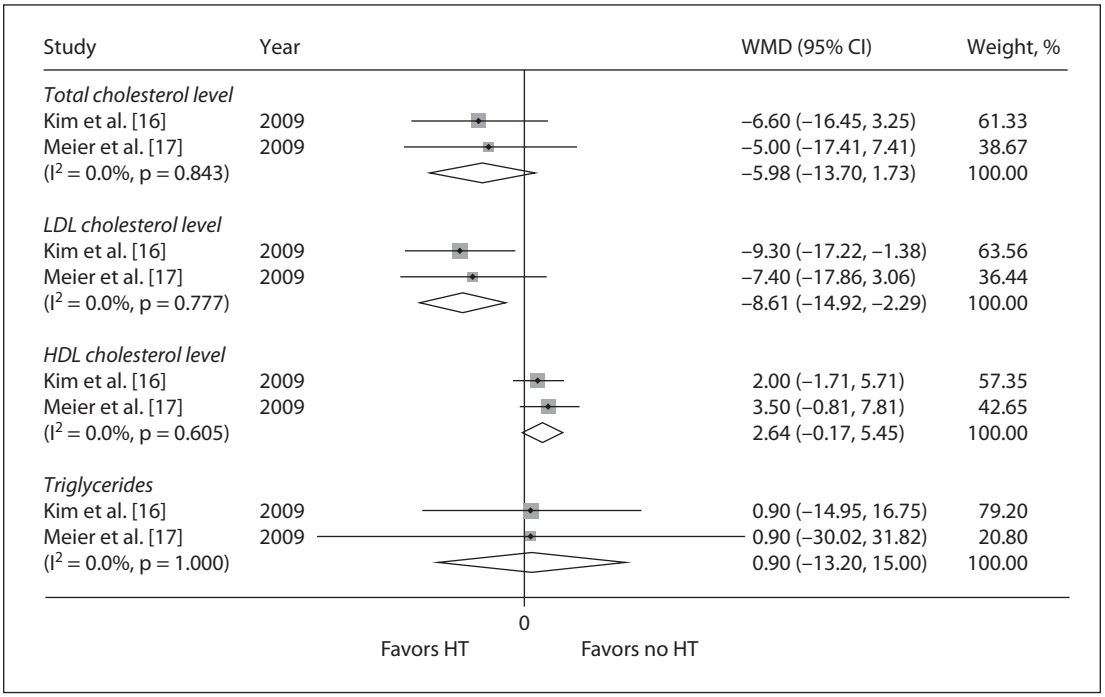

Fig. 2. Influence of lipid profiles on HT risk in ischemic stroke patients.

Table 4. Method of the analysis

	Bang et al. [13] 2007 (n = 104)	Montaner [14] 2008 (n = 60)[a]	Uyttenboogaart et al. [15] 2008 (n = 252)[b]	Kim et al. [16] 2009 (n = 377)	Meier et al. [17] 2009 (n = 311)	Restrepo et al. [18] 2009 (n = 142)	Bang et al. [19] 2009 (n = 26)[c]	Paciaroni et al. [20] 2009 (n = 491)[d]
Missing data, %								
HT	0	0	0	0	0	0	0	0
Total cholesterol	?	0	0	0	1	?	?	NA
LDL cholesterol	13	0	0	6.9	10.9	?	?	?
HDL cholesterol	?	0	0	6.9	6.7	NA	?	NA
Triglycerides	?	0	0	6.9	5.4	NA	NA	NA
Lipids levels presented as continuous variables	+	+	+	+	+	+	+	+
Comparison of 2 groups with and without								
$_{all}$HT	–	–	–	+	+	–	–	–
$_{s}$HT	+	+	+	–	+	–	–	–
Multivariate analysis with								
HT as dependent variable	+	–	+	+	+	–	–	–
Lipid levels as independent variables	+	–	+	+	+	–	–	–

+ = Characteristics fulfilled; – = characteristics not fulfilled; ? = unknown; NA = not applicable.
[a] Among 145 patients, 60 were evaluated for the association between HT and lipid profile.
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Table 5. Comparison of lipid profiles in patients with and without HT

	HT				p values	Multivariable analysis OR (95% CI)
	present		absent			
	n	mean (SD)	n	mean (SD)		
Any type of HT						
Total cholesterol level						
Kim et al. [16], 2009	74	176.08 (38.31)	303	182.66 (40.63)	0.210	0.85 (0.64–1.12) for 38.67 mg/dl increase
Meier et al. [17], 2009	64	197.60 (44.85)	247	202.63 (46.04)	0.418	NR
LDL cholesterol level						
Kim et al. [16], 2009	74	104.87 (30.18)	303	114.16 (34.83)	0.045	0.72 (0.51–1.03) for 38.67 mg/dl increase
Meier et al. [17], 2009	64	112.14 (37.89)	247	119.49 (38.67)	0.220	NR
HDL cholesterol level						
Kim et al. [16], 2009	74	45.27 (15.09)	303	43.34 (12.38)	0.660	NR
Meier et al. [17], 2009	64	56.45 (15.85)	247	52.97 (14.69)	0.111	NR
Triglycerides						
Kim et al. [16], 2009	74	116.02 (61.99)	303	115.14 (63.77)	0.890	NR
Meier et al. [17], 2009	64	156.76 (113.36)	247	155.88 (108.94)	0.839	NR
Symptomatic HT						
Total cholesterol level						
Bang et al. [13], 2007	17	141.40 (40.9)	87	173.30 (39.2)	0.005	NR
Montaner [14], 2008	5	215.94	55	221.80	0.860	NR
Uyttenboogaart et al. [15], 2008	13	197.22 (46.40)	239	197.22 (46.40)	0.900	0.73 (0.40–1.34) for 38.67 mg/dl increase
Meier et al. [17], 2009	15	197.60 (46.40)	247	202.63 (46.04)	0.720	NR
LDL cholesterol level						
Bang et al. [13], 2007	17	77.90 (40.5)	87	106.00 (32.5)	0.006	0.96 (0.941–0.995) for 38.67 mg/dl increase
Montaner [14], 2008	5	139.05	55	135.53	0.820	NR
Uyttenboogaart et al. [15], 2008	13	116.01 (30.94)	239	119.88 (38.67)	0.030	NR
Meier et al. [17], 2009	15	113.68 (35.18)	247	119.49 (38.67)	0.548	NR
HDL cholesterol level						
Bang et al. [13], 2007	17	45.30 (13.6)	87	47.60 (12.3)	0.526	NR
Montaner [14], 2008	5	49.70	55	56.63	0.270	NR
Uyttenboogaart et al. [15], 2008	13	38.67 (11.60)	239	46.40 (19.34)	0.730	NR
Meier et al. [17], 2009	15	59.55 (18.17)	247	52.97 (14.69)	0.205	NR
Triglycerides						
Bang et al. [13], 2007	17	97.90 (42.1)	87	103.50 (69.4)	0.772	NR
Montaner [14], 2008	5	135.94	55	148.14	0.660	NR
Uyttenboogaart et al. [15], 2008	13	221.43 (150.57)	239	159.43 (97.43)	0.020	2.16 (1.20–3.91) for 88.57 mg/dl increase
Meier et al. [17], 2009	15	164.74 (117.79)	247	155.88 (108.94)	0.951	NR

Lipid levels are provided in mg/dl. n = Number of patients; NR = not reported.

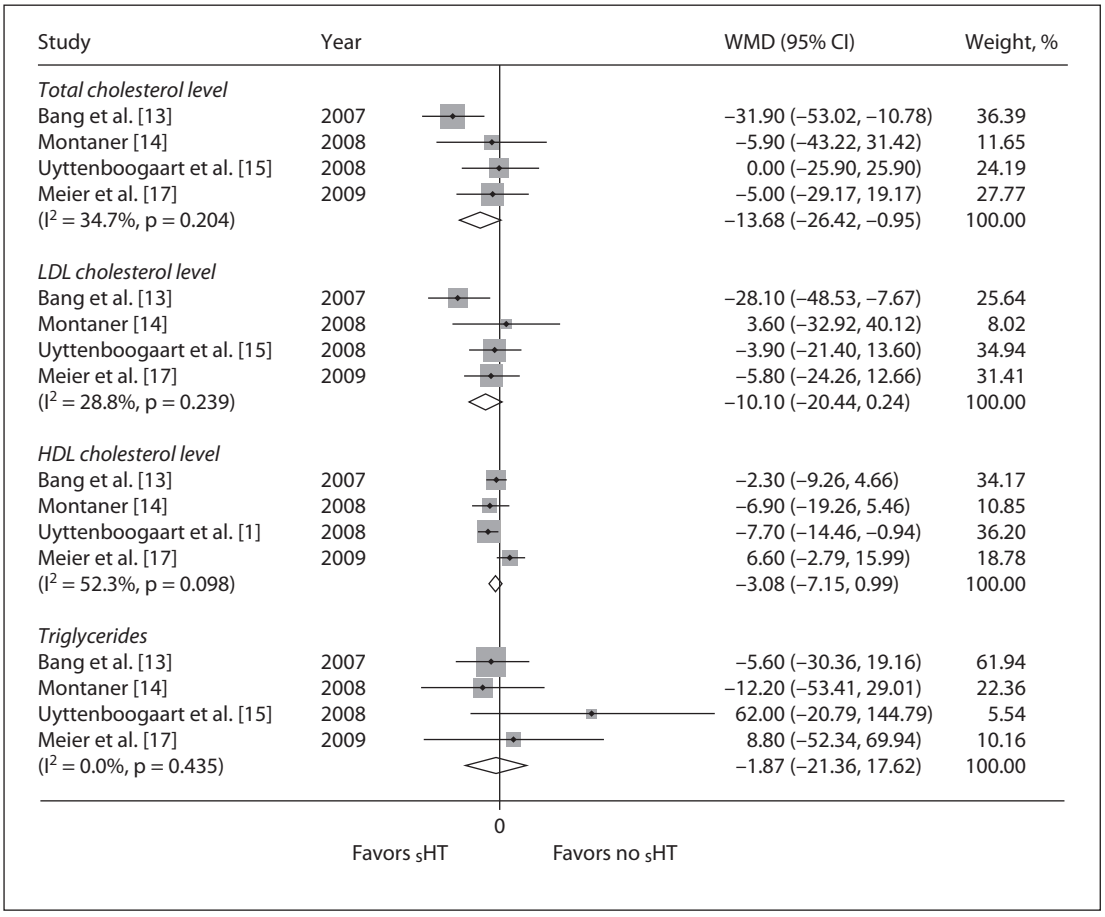

Fig. 3. Influence of lipid profiles on the risk of $_s$HT in ischemic stroke patients.

Perspective

This systematic review suggests that patients with low LDL cholesterol levels have an increased risk of HT, but is not conclusive for the influence of HDL, and suggests no influence of triglyceride levels. The results of the meta-analysis are limited by methodological issues: (i) lipid profiles were not determined specifically to address the question of the relationship with HT in 7 studies and were heterogeneously assessed; (ii) no study was conducted to test the hypothesis that is the subject of this meta-analysis, and (iii) heterogeneity for the method of assessment of HT and unclear definition of HT or of its symptomatic presentation. Therefore, there is a risk that unmeasured biases could have affected the results.

The main limitations of this study are that: (i) none of them was designed to address the study question; (ii) the HT definitions were not consistent among studies, and (iii) there were significant issues related to the measurement of lipid parameters. Therefore, these limitations of the data make conclusion quite weak unless confirmed by another large and properly designed study. The questions that should be addressed now are: (i) what is the mechanism of this increased risk of HT with low levels of LDL? (ii) Do statins contribute to the increased risk of HT or do anti-inflammatory properties of statins counterbalance this effect? (iii) Are these results valid in patients who were treated with rt-PA? Prospective studies recruiting non-selected ischemic stroke patients (treated or not by rt-PA) and designed specifically for that purpose as well as studies in animal models are required to solve these issues.

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Disclosure Statement

None.

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