

Evaluation of C-Reactive Protein Measurement for Assessing the Risk and Prognosis in Ischemic Stroke A Statement for Health Care Professionals From the CRP Pooling Project Members

Mario Di Napoli, MD; Markus Schwaninger, MD; Roberto Cappelli, MD; Elena Ceccarelli, MD; Giacinto Di Gianfilippo, MD; Cristina Donati, MD; Hedley C.A. Emsley, PhD, MRCP; Sandro Forconi, MD; Stephen J. Hopkins, PhD; Luca Masotti, MD; Keith W. Muir, MD, FRCP; Anna Paciucci, MD; Francesca Papa, MD; Sabina Roncacci, MD; Dirk Sander, MD; Kerstin Sander, MD; Craig J. Smith, MD, MRCP; Alessandro Stefanini, MD; Daniela Weber, MD

Background and Purpose—Several studies have shown, in different populations, that modest elevation of plasma C-reactive protein (CRP) in the range seen in apparently healthy individuals is a strong predictor of future vascular events. Elevated plasma CRP concentrations are also associated with an increased risk of cerebrovascular events and an increased risk of fatal and nonfatal cardiovascular events in ischemic stroke patients. These epidemiological and clinical observations suggest that determination of plasma CRP concentrations could be used as an adjunct for risk assessment in primary and secondary prevention of cerebrovascular disease and be of prognostic value. The aim of this review is to summarize the evidence for CRP as an independent predictor of cerebrovascular events in at-risk individuals and ischemic stroke patients and to consider its usefulness in evaluating prognosis after stroke.

Summary of Review—CRP fulfils most of the requirements of a new risk and prognostic predictor, but several issues await further confirmation and clarification before this marker can be included in the routine evaluation of stroke patients and subjects at risk for cerebrovascular disease. Potentially important associations have been established between elevated plasma CRP concentrations and increased efficacy of established therapies, particularly lipid-lowering therapy with statins.

Conclusion—At present, there is not sufficient evidence to recommend measurement of CRP in the routine evaluation of cerebrovascular disease risk in primary prevention, because there is insufficient evidence as to whether early detection, or intervention based on detection, improves health outcomes, although shared risk of cardiovascular disease indicates this may be of value. In secondary prevention of stroke, elevated CRP adds to existing prognostic markers, but it remains to be established whether specific therapeutic options can be derived from this. (*Stroke*. 2005;36:1316-1329.)

Key Words: aspirin ■ cerebrovascular disorders ■ inflammation ■ meta-analysis ■ mortality ■ prevention ■ risk factors ■ scientific statements

Stroke is an important health issue for individuals and society. Thus, early identification of those at increased risk of stroke should represent a significant contribution to health improvement so that interventions can be targeted to those most likely to benefit. Because stroke risk prediction based only on conventional risk factors such as blood

pressure (BP) is still not completely reliable, a continued search for predictive markers is of interest.

Considerable interest has focused on the role of inflammatory processes in atherothrombosis and the ischemic complications associated with this. C-reactive protein (CRP), a peripheral marker of inflammation, has consistently been observed to be

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From the Neurological Service (M.D.N., G.D.G., A.P., S.R., A.S.), San Camillo de Lellis General Hospital, Rieti, Italy; Neurologische Klinik (M.S., DW.), University of Heidelberg, Heidelberg, Germany; the Department of Internal (R.C., E.C., C.D., S.F.), Cardiovascular, and Geriatric Medicine, University of Siena, Siena, Italy; Division of Neuroscience (H.C.A.E.), University of Liverpool, The Walton Centre for Neurology & Neurosurgery, Liverpool, UK; Injury Research (S.J.H.), University of Manchester and Hope Hospital, Salford, UK; Internal Medicine (L.M.), Cecina Hospital, Cecina, Livorno, Italy; the Division of Clinical Neurosciences (K.W.M.), University of Glasgow, Institute of Neurological Sciences, Southern General Hospital, Glasgow, Scotland, UK; SMDN—Center for Cardiovascular Medicine and Cerebrovascular Disease Prevention (F.P.), Sulmona, L'Aquila, Italy; the Department of Neurology (D.S., K.S.), Technical University of Munich, Munich, Germany; and the Division of Medicine and Neurosciences-Hope (C.J.S.), University of Manchester, Hope Hospital, Salford, UK.

Correspondence to Mario Di Napoli, MD, Neurological Section, SMDN—Center for Cardiovascular Medicine and Cerebrovascular Disease Prevention, Via Trento, 41, 67039-Sulmona, L'Aquila, Italy. E-mail mariodinapoli@katamail.com

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related to the risk of cerebrovascular and cardiovascular (CV) events^{1–10} and is consistently elevated in the circulation of patients after acute ischemic stroke,^{11–20} even when factors known to be associated with raised CRP concentrations such as infection and atherosclerosis are taken into account.²⁰ These important clinical data are also supported by abundant laboratory and experimental evidence demonstrating that atherothrombosis represents a chronic inflammatory process.²¹

Before measurement of this novel vascular risk indicator is introduced into routine clinical practice, however, it is important to examine critically the predictive role of CRP in primary and secondary stroke risk. This should clarify other determinants of CRP in plasma, evaluate the cost-effectiveness of measuring CRP, and identify the role of CRP in cerebrovascular pathogenetic mechanisms to facilitate the development of potential new pharmacological treatments. In January 2003, the Centers for Disease Control and Prevention (CDC) and the American Heart Association (AHA) released a statement for health care professionals concerning markers of inflammation in cardiovascular disease (CVD) and their application to clinical and public health practice.²² This statement included a description of characteristics deemed desirable in peripheral inflammatory markers, including CRP, for their use in CVD risk prediction. This guideline concluded that there was evidence in favor of the usefulness and efficacy of testing CRP in certain patients, but that mass population screening was unwarranted. They recommended plasma CRP measurement as an adjunct to use of established risk factors for assessing the risk of coronary heart disease (CHD) in persons with a calculated 10-year CVD risk of 10% to 20%.²² The role of plasma CRP in predicting cerebrovascular events in at-risk individuals or stroke patients received less attention in the CDC/AHA document. Specific statements regarding its use in this context were not made in the statement or in the more recent report from the Clinical Practice Discussion Group.²³ In December 2003, a European study group was formed to review the scientific evidence relating CRP measurement to stroke risk assessment in subjects at risk for cerebrovascular disease and in stroke patients. This group was established on a voluntary and on-demand basis among active and independent European researchers in the field to avoid any actual or potential conflicts of interest. An Internet-based technology was used during the editorial process. A MEDLINE database search to identify relevant published primary literature and reviews was conducted by the co-chairs, whereas the recommendations of this document are derived from contributions by the entire group. The purpose of this CRP Pooling Project Special Report is to review evidence and logic that bear on the potential usefulness of CRP measurement for the evaluation of cerebrovascular disease risk in primary and secondary prevention. The US Surgeon General's criteria for inference of causality were applied when examining the evidence—namely, the strength, temporality, dose–response relationship, biological plausibility, and consistency of the findings.²⁴ The quality of scientific evidence for an association was assessed,²⁵ and the American College of Cardiology/AHA classification of recommendations and levels of evidence were used (see Appendix). An evidence-based approach was used to consider the recom-

mendations for applying CRP as a screening tool.²⁶ This statement summarizes the major findings and conclusions of the study group. It has been reviewed and approved by all members, considers the best available evidence for an association between CRP and cerebrovascular disease, and represents an extension of AHA/CDC recommendations in respect of cerebrovascular disease.

Biology and Pathophysiology of CRP

CRP is a trace protein in the circulation of healthy subjects, with a median concentration of ≈ 1 mg/L. As the prototypical member of the acute phase proteins, however, concentration can increase 100-fold or more in response to injury, infection, or inflammation. Acute phase phenomena may also accompany chronic inflammatory disorders. Moderately increased plasma CRP concentrations are found in smokers and under conditions of atherosclerosis, psychological stress, diabetes, and obesity, and in the elderly.^{8,27}

CRP is produced mostly by liver hepatocytes in response to cytokines such as interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor.^{28,29} Cogent data suggest that it is produced in the atherosclerotic lesion (especially by smooth muscle cells and macrophages), the kidney, neurons, and alveolar macrophages.³⁰ IL-6 is almost certainly the primary circulating physiological mediator, because most other cytokines rarely reach effective concentrations in plasma. Whereas CRP concentrations generally reflect the expression of IL-6, plasma concentrations of CRP are more stable than those of IL-6. Induction of CRP is rapid and the half-life (19 hours) is long enough for a steady time course in repeated measurement.³¹ There does not appear to be any diurnal variation,³² by contrast with other acute phase components.³³ These properties make plasma CRP very useful for the diagnostic workup of inflammatory and infectious diseases.

CRP is a member of the pentraxin protein family^{31,34} and comprises 5 identical protomers that are highly conserved in evolution. CRP was discovered and named in 1930 as a protein reacting with the C-polysaccharide of the cell wall of *Streptococcus pneumoniae*. Phosphorylcholine residues of the C-polysaccharide provide the major determinant for interaction with CRP.³⁴ CRP binding to the bacterial cell wall is presumed to be involved in innate immunity because CRP protects mice against *S. pneumoniae* infection.^{35–37}

The physiological role of CRP is poorly understood and it has several potentially anti-inflammatory properties as well as pro-inflammatory effects. These may contribute to the progression of atherothrombosis and the development of ischemic injury associated with atherothrombotic complications.^{38–40}

Ligand-bound CRP activates the classical complement pathway,³⁶ binds to immunoglobulin receptors on immune cells, and activates cytokine production and complement related inflammatory reactions that may exacerbate inflammatory ischemic injury.^{41–43} Moreover, CRP induces various inflammatory changes in endothelial and smooth muscle cells that have been associated with atherosclerosis.⁴⁴ It binds to nuclear components, damaged membranes, and apoptotic cells.^{45,46} Interestingly, it binds to oxidized low-density lipoproteins (LDL) in which phosphorylcholine is the principal

phospholipid.⁴⁶ The complex of CRP and LDL is opsonized by macrophages, resulting in the generation of foam cells.³⁸ It induces expression of the adhesion molecules E-selectin, vascular cell adhesion molecule-1, and intercellular adhesion molecule-1 by endothelial cells, and may help recruit monocytes by virtue of inducing monocyte chemoattractant protein-1.⁴⁷ CRP is associated with endothelial cell dysfunction and progression of atherosclerosis, possibly by decreasing nitric oxide synthesis.⁴⁸ It also has the ability to sensitize endothelial cells to being destroyed by cytotoxic CD4⁺ T cells,⁴⁹ and to facilitate thrombogenesis through stimulation of tissue factor biosynthesis by macrophages. This suggests that high CRP plasma concentrations and the extent of its deposition in the atherosclerotic plaque are associated with plaque vulnerability and the occurrence of acute thrombotic events.^{49,50} Recently, a proatherogenic role of CRP was also described in apolipoprotein E-deficient mice.⁵¹ It is therefore conceivable that CRP not only acts as a marker but also is involved in the initiation and progression of atherosclerosis.

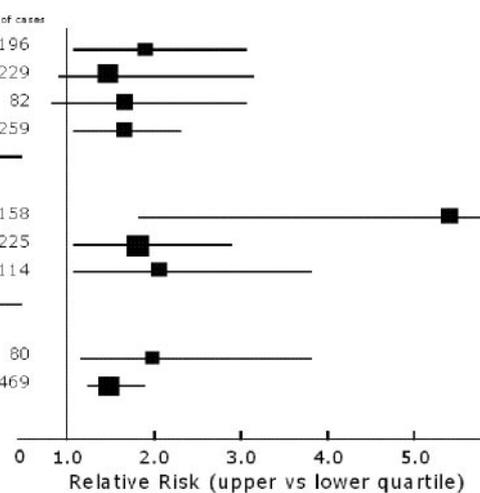
CRP and Risk of Vascular Disease

Raised plasma concentrations of CRP are associated with atherosclerosis of carotid, coronary, or lower limb peripheral arteries,^{28,52} and with progression of atherosclerotic disease.⁵² The earliest studies of CRP and future vascular events were reported in 1996 and 1997, and showed an increased risk of future coronary events and stroke.⁵³ The strength of CRP as a predictor in relation to other risk factors (such as LDL cholesterol, other inflammatory markers, and novel markers such as the metabolic syndrome and the global vascular risk measured by the Framingham Coronary Heart Diseases Risk Score) has been subsequently evaluated.⁵³ CRP is an indicator of the risk for future CV events and is independent of other established risk factors such as hypercholesterolemia and cigarette smoking in apparently healthy and at-risk populations. A meta-analysis of prospective population-based studies before 2000 compared people in the top third of CRP measurements with people in the bottom third and found an odds ratio for future CHD of 2.13 (95% confidence interval, 1.38 to 3.28).⁵⁴ It appears that it is on the basis of these data that the CDC and the AHA issued guidelines in 2003 for the use of high sensitivity CRP (hsCRP) in clinical practice.²² This statement recommends that: (1) an hsCRP assay is the assay of choice and should be performed in metabolically stable persons without obvious inflammatory or infectious diseases; (2) the results should be expressed in mg/L and 2 assays, averaged, fasting or nonfasting, 2 weeks apart, represent the inflammatory status better; (3) the adult population should be stratified in 3 tertiles, at different CV risk: low risk (CRP concentration <1.0 mg/L), average risk (1.0 to 3.0 mg/L), high risk (>3.0 mg/L); (4) persons at high risk have ≈2-fold increased risk of future CVD compared with those in the lower tertile; and (5) the patients with moderate risk (10% to 20% risk of CHD over 10 years) may benefit from measurement of CRP in addition to traditional CV risk factors. In this case, measurement of hsCRP may direct further examinations or therapy for primary prevention of CVD, although the benefit of this strategy is uncertain. In the

patients at low and high risk, measurement of hsCRP contributes very little.

Furthermore, there is still controversy over the degree of risk conferred by elevated CRP concentrations. A recent large study on the role of CRP in the prediction of CHD concluded that the predictive value of CRP is moderate compared with classical risk factors.⁹ After adjustment for risk factors such as smoking status, BP, body mass index, and total cholesterol concentration, patients with a CRP concentration in the top third (cutoff value, 2.0 mg/L) had a relative risk of CHD of 1.45 (95% confidence interval, 1.25 to 1.68) as compared with patients whose values were in the bottom third.⁹ Doubts have been raised as to the validity of the methodology of this study, because CRP is correlated with many known CHD risk factors, and the contribution of CRP to the improvement of any prediction model of CHD would depend on exactly which other variables are included in the model.⁵⁵ However, in any analysis in which CRP is independently statistically significantly associated with CHD outcomes, it follows logically that measures of prediction such as area under the receiver-operating characteristic curve would always be better with inclusion of CRP than without it.^{15,56} These recent findings highlight the need to reconsider the AHA/CDC recommendations. The data on CRP in CHD are strong and persuasive, but questions raised over the data suggest prudence in an extensive use of CRP testing in cerebrovascular disease without analysis of the need for specific studies in this area. Despite the view of atherosclerosis as a single disease, the risk factor profiles of stroke and myocardial infarction clearly differ in important respects: stroke and CHD affect different patient populations (older age in stroke), there is only a partial overlap in the pathogenesis (atherothrombosis is the first but not the only cause of stroke), and stroke and CHD have different risk factor profiles (high cholesterol concentrations are stronger risk factor in CHD, whereas arterial hypertension is more important in stroke). Given that stroke is not a pathologically uniform condition, some mechanistic insights about the role of inflammation may well come from going beyond the crude separation into hemorrhage and ischemia and looking at stroke subtypes. If evidence of inflammation signifies atherogenesis, for example, then a distinction between lacunar syndromes and carotid disease could be anticipated.⁵⁷ Several studies have focused on the relationship between CRP concentration and carotid atherosclerosis. The main conclusions of these studies, with only few discordant findings,⁵⁸ have demonstrated that high concentrations of plasma CRP in subjects with symptomatic or asymptomatic carotid stenosis, whether surgically treated or not, are associated with increased intima-media thickness, development, progression, rupture of atherosclerotic plaques, and subsequent cerebrovascular events.^{52,59–70} Less evident and inconsistent data are present for cerebral small vessel disease and lacunar stroke.⁷¹ Therefore, it is not possible to transfer concepts that are valid for CHD directly to stroke. However, researchers have proposed that assessment of CRP concentrations may provide a useful method to assess cerebrovascular risk, thus improving treatment decisions and, ultimately, patient outcomes.

Men	End-point	Degree of adjustment	No. of cases
PHS (Ridker, 1997)	IS	+++	196
NHANES III (Ford, 2000)	SR-S	+++	229
Framingham (Rost, 2002)	TIA+IS	+++	82
HHP (Curb, 2003)	IS	+++	259
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Women	End-point	Degree of adjustment	No. of cases
WHS (Ridker, 1998, 2000, 2002)	MI or IS	+++	158
NHANES III (Ford, 2000)	SR-S	+++	225
Framingham (Rost, 2002)	TIA+IS	+++	114
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Elderly	End-point	Degree of adjustment	No. of cases
Leiden-85P (Guzzetta, 2000)	FS	+++	80
CHS (Cao, 2003)	IS	+++	469



ham, Framingham Heart Study; HHS, Honolulu Heart Study; WHS, Women’s Health Study; Leiden-85P, Leiden Heart Study; and CHS, Cardiovascular Health Study.^{1,3–8,56,72–74} Adapted from Di Napoli and Papa.¹⁹³

Primary Prevention of Stroke: The Role of CRP in Stroke Risk Assessment

Several prospective studies have demonstrated that a single, nonfasting measurement of CRP in apparently healthy individuals is a predictor of future fatal and nonfatal cerebrovascular events (Figure).^{1,3–8,56,72–74}

The relationship between a patient’s baseline concentration of CRP and future cerebrovascular risk has been consistent in different studies and in most cases has proven to be independent of age, smoking, cholesterol concentrations, BP, and diabetes, the major risk factors evaluated in daily clinical practice. These effects are present in women and men, the elderly and middle-aged, smokers and nonsmokers, and those with and without diabetes mellitus. The value of CRP for assessing cerebrovascular risk remains significant after adjustment for the risk factors typically used in global risk-assessment programs.⁷⁵

However, whereas analyses from these studies provide information about relative risks, we know little or nothing about predictive values and absolute risk for cerebrovascular disease.⁷⁶ Thus, we do not know what the actual risk for cerebrovascular disease is in a given individual with modestly elevated serum CRP. We do not know what the likelihood of a false-positive result is, ie, how many individuals are incorrectly identified as being likely to have cerebrovascular disease. This information would be important to estimate cost-effectiveness before undertaking large-scale screening or interventions. Lack of information on the absolute risk and the cost of screening strategies indicates the need for further assessment of these questions. In most studies that have examined patients before development of CVD, the design has involved retrospective measurement of a factor of interest in baseline samples many years after study entry and once a sufficient number of events had accrued. Few studies have therefore been able to adjust for issues such as regression to the mean for either novel factors (such as CRP) or for conventional factors (such as BP). It is not known whether a single measurement should define risk categorization, or whether repeated measurements enhance risk stratification. In addition, it is not possible to evaluate the relationship of risk factors with CRP over time. In a study that looked at a panel of

Prospective studies relating baseline plasma C-reactive protein (CRP) levels to the risk of first cerebrovascular event. Relative risk compares top and bottom quartile of baseline measurements. Black squares indicate the relative risk in each study, with the size of square proportional to number of cases. All studies were adjusted for standard vascular risk factors. The key observation in all these studies is that the level of CRP is consistently associated with increased cerebrovascular risk in several different population groups, both at low and at high absolute risk for these events. IS indicates ischemic stroke; SR-S, self-reported stroke; TIA, transient ischemic attack; MI, myocardial infarction; FS fatal stroke; PHS, Physicians’ Health Study; NHANES III, 3rd National Health and Nutrition Examination Survey; Framing-

ham, Framingham Heart Study; HHS, Honolulu Heart Study; WHS, Women’s Health Study; Leiden-85P, Leiden Heart Study; and CHS, Cardiovascular Health Study.^{1,3–8,56,72–74} Adapted from Di Napoli and Papa.¹⁹³

inflammatory proteins, which did not include CRP, there was a potential interaction of inflammation and BP over time: those subjects with evidence of inflammation not only had higher BP at study entry but also were more likely to have a greater BP increase over time than those without increased markers of inflammation.⁷⁷ Whether such a relationship exists for CRP is not known.

At the moment it is unclear which CRP values identify different grades of cerebrovascular disease risk with respect to tertiles established by the AHA/CDC statement for CHD. In particular it is unclear if the same tertiles used for CHD could stratify the same grades of risk for cerebrovascular disease in the general population. Table 1 summarizes quartiles and tertiles of CRP values and the associated probability of a cerebrovascular event. The studies were consistent in their finding of a concentration-dependent relationship between the concentration of CRP and the risk of incident stroke. Broad representation for sex and age was present in these studies for men, women, and older adults.^{1,3–8,56,72–74}

Using the Framingham Coronary Heart Diseases Risk Score, a simplified coronary prediction tool performed for estimating CV risk in middle-aged individuals, it was noticed that CRP concentrations were significantly associated with the levels of risk for CHD in men and in women not taking estrogen therapy, but CRP was correlated only minimally with individual components of the Framingham Coronary Heart Diseases Risk Score. This may be explained by CRP having an adjunctive role in the global risk of CVD.⁷⁸ At the present, there are no similar studies on global risk prediction in stroke so it is difficult to suggest CRP as a potential adjunct in the global prediction of stroke risk. Furthermore, the Framingham Coronary Heart Diseases Risk Score is of little value for stroke prevention because it places considerable emphasis on cholesterol concentration, which is a relatively minor risk factor for ischemic stroke.

Secondary Prevention of Stroke: The Role of CRP in the Risk Assessment of Recurrent Vascular Events

In secondary prevention, the role of CRP is evolving rapidly. Multiple studies demonstrate that CRP concentrations are

TABLE 1. Adjusted* Probability for Stroke Using Quartiles or Tertiles of CRP in Primary Prevention Studies

Study	Quartiles of CRP Values (mg/L)			
	Lowest	Low-Moderate	Moderate-High	Highest
PHS	<0.55 (RR1.0)	0.56–1.14 (RR 1.7)	1.15–2.10 (RR 1.7)	>2.11 (RR 1.9)
WHS†	<1.5 (RR1.0)	1.5–3.7 (RR 2.7)	3.8–7.3 (RR 3.5)	>7.3 (RR 5.5)
Framingham males	<1.10 (RR1.0)	1.10–3.00 (RR 0.9)	3.10–6.80 (RR 1.5)	>6.90 (RR 1.6)
Framingham females	<1.10 (RR1.0)	1.10–3.00 (RR 1.2)	3.10–6.80 (RR 1.6)	>6.90 (RR 2.1)
CHS	<1.12 (HR1.0)	1.12–2.05 (HR1.19)	2.05–4.30 (HR1.05)	>4.30 (HR1.60)
HHP	0.10–0.32 (RO 1.1)	0.32–0.54	0.55–1.00	>1.01 (RO 2.4)

Study	Tertiles of CRP values (mg/L)		
	Low	Moderate	High
NHANES III	<2.1 (OR 1.26)	2.1–5.5 (OR 1.58)	>5.5 (OR 2.21)

PHS indicates Physician' Health Study; WHS, Women's Health Study; NHANES, Third National Health and Nutrition Examination Survey; Framingham, Framingham Health Study; CHS, Cardiovascular Health Study; HHP, Honolulu Heart Program; RR, relative risk; OR, odds ratio; HR, hazard ratio; RO, relative odds.

*Adjusted risk for traditional cardiovascular risk factors.

†Risk of combined myocardial infarction and stroke.

predictive of future CVD events in stroke patients and are independent of the predictive value of conventional prognostic markers (Table 2).^{10–15,17–19,79–84} Importantly, plasma CRP concentrations in ischemic stroke patients predict outcome or new vascular events independently of age, stroke severity, and other prognostic factors.^{10,11,13–15,17–19,79–84} Further, knowledge of inflammatory status has been shown to be effective in distinguishing between patient subgroups more or less likely to benefit from an aggressive versus conservative management approach.⁸⁵ However, appropriate clinical cutoff points for CRP in the setting of acute ischemic stroke have not yet been defined, nor has timing of CRP evaluation in relation to the onset of the qualifying event been determined.

Although no large study has prospectively assessed the value of CRP for prognostic short-term and long-term stratification of patients with ischemic stroke, many data suggest that CRP might be of value in this group of patients.^{10,11,13–15,17–19,79–81} All studies are characterized by a relatively small sample size, but almost all have a prospective assessment of CRP concentrations before occurrence of outcomes, objective assessment of outcomes without knowledge of CRP concentrations, and control of potentially confounding variables. Obviously it is difficult to compare findings across studies because the measure of association used, and the specific potential confounders adjusted for, vary between the studies. However, the majority of the studies show an increase in risk of death or new CV events as CRP concentration increases, and the increase in risk persists despite adjustment for several traditional cerebrovascular risk factors and for stroke severity.

However, the data are less consistent for the in-hospital prognostic stratification of these patients. In the acute phase, evaluation is confounded by the common coexistence of infection, either as an (often unrecognized) antecedent to, or complication of stroke, or of other stimuli for an inflammatory response (eg, deep vein thrombosis, which may be present radiologically in up to 20% of patients).⁸⁷ High concentrations of CRP in the acute phase of ischemic stroke

may reflect the extent of cerebral tissue injury, systemic infection, or inflammatory disease.⁸⁸

Secondary Prevention of Stroke: What Is the Role of CRP as a Prognostic Marker in Ischemic Stroke Patients?

In the acute phase of stroke, inflammation contributes to brain damage initiated by ischemia.⁸⁹ The inflammatory cascade is mediated by an increasing concentration of local cytokines, adhesion molecules, acute phase proteins, macrophages, and leukocytes and the strength of this response is related to early and late clinical outcomes.⁹⁰ The hypothesis that high concentrations of CRP in the acute phase of stroke could reflect the extent and severity of cerebral injury has been tested in laboratory and clinical settings. A very recent study found that treatment of rats with human CRP resulted in larger cerebral infarcts after middle cerebral artery occlusion, demonstrating that CRP contributes to brain damage induced by ischemia.⁹¹ Plasma concentrations can increase quite rapidly after stroke.^{20,85} In clinical settings, it has been observed that higher concentrations of CRP were associated with larger brain infarcts.^{15,82} Moreover, some reports have reported a positive association between CRP values and stroke severity or neurological disability.^{12,15,17–19,80,82}

Although single measures of CRP taken within 72 hours of stroke onset are of prognostic value in selected populations, the value of this in patients with concurrent infection or other inflammatory comorbidities has not been established and the optimal timing and number of repeat samples also not determined. In the presence of overt inflammatory disease or infection, data should be interpreted cautiously and possibly CRP titration repeated after the underlying acute insult has resolved for long-term stratification purposes. We would certainly recommend the further assessment of patients with highly elevated CRP concentrations for identification of causes of inflammation unrelated to cerebrovascular disease.

TABLE 2. C-Reactive Protein Levels and Outcome in Ischemic Stroke

Author	Patients	(Primary) Endpoint	Follow-up	Detection Limit	Time of CRP Determination	Results
Canova et al, 1999 ¹²	138 patients with TIA, ischemic or hemorrhagic stroke	Neurological deficit	NA	2.4 mg/L	On admission, <120 h after onset of symptoms	No significant correlation between CRP values and prognosis
Muir et al, 1999 ¹¹	228 patients with acute ischemic stroke	Survival	959 d (average)	2.5 mg/L	<72 h after onset of symptoms	CRP is an independent predictor of survival
Di Napoli et al, 2001 ^{1,3,14,15}	193 patients with first ever ischemic stroke	Combined vascular endpoint (death or any new vascular event)	12 mo	0.175 mg/L	<24 h, 48–72 h after onset of symptoms, at discharge	CRP is an independent risk factor for a bad outcome, determination at discharge has the highest predictive value
Di Napoli and Papa, 2001 ⁷⁹	193 patients with first ever ischemic stroke	Combined vascular endpoint (death or any new vascular event)	24 mo	0.175 mg/L	<24 h after onset of symptoms	Statins lower CRP concentration and the risk for new vascular events
Anuk et al, 2002 ¹⁷	60 patients with first acute ischemic stroke	NIHSS, mRS	8–12 mo	0.175 mg/L	Within 24 h after acute event	CRP on admission correlated with neurological deficit on follow-up
Winbeck et al, 2002 ¹⁹	127 patients with first ischemic stroke	Barthel index and mRS, combined vascular endpoint	12 mo	0.1 mg/L	<24 h after onset of symptoms	CRP within 24 h predicts unfavorable outcome
Iyigun & Bakirci, 2002 ⁸⁰	83 patients with first ischemic stroke and 43 age-matched controls	GOS	NA	NA	<72 h after onset of symptoms	Patients with large infarcts in the middle cerebral artery and anterior cerebral artery had higher fibrinogen and CRP concentrations than the control group
Ceccarelli et al, 2002 ¹⁸	Retrospective analysis of 288 elderly patients with acute stroke	mRS, length of hospital stay, mortality, rate of rehospitalization	12 mo	0.175 mg/L	<12 h after admission	CRP on admission correlated with 30-d mortality, disability at discharge, and the rate of rehospitalization for secondary stroke
Arenillas et al, 2003 ¹⁰	71 patients with first ischemic event plus intracranial stenosis	Cerebral ischemic events, myocardial infarction	12 mo	0.175 mg/L	>8 mo after acute vascular event	CRP levels >14 mg/L were associated with increased risk for ischemic event-related intracranial large artery occlusive disease
Guo et al, 2003 ⁸¹	121 patients with acute ischemic stroke	Neurological deficit, carotid plaque, subtype of stroke	NA	NA	<72 h after onset of symptoms	Higher CRP concentrations on admission correlated with leukocyte count and blood glucose level, larger infarct, occurrence of carotid plaques, severe neurological deficit, and worse outcome
Smith et al, 2004 ⁸²	37 patients with acute ischemic stroke	NIHSS, mRS, BI, infarct volume;	3 and 12 mo	0.1 mg/L	Peak concentration measured between presentation and 5–7 d	Peak CRP correlated strongly with stroke severity and infarct volume at 5–7 d, and disability at 3 and 12 mo
Silvestri et al, 2004 ⁸³	150 elderly patients with atherothrombotic ischemic stroke	Mortality and new cardiac and cerebrovascular events	Mean±SD 16±5 mo	NA	<12 h, 72 h after onset of symptoms, at discharge	CRP was predictor of future in-hospital and 3-mo future cerebrovascular events, whereas it was not related to 1-y prognosis
Christensen et al, 2004 ⁸⁴	716 patients with ischemic stroke, intracerebral haemorrhage, or transient ischemic attacks	SSS, 7-d, 3- and 12-mo mortality, and 3- and 12-mo disability	3 and 12 mo	NA	<24 h after admission	CRP levels increase in the first 24 h in severe stroke and correlates with disability measured with mRS and mortality for all causes 3 and 12 mo after stroke

mRS indicates modified Rankin score; BI, Barthel Index; GOS, Glasgow Outcome Scale; NIHSS, NIH Stroke Scale Score; SSS, Scandinavian Stroke Scale; NA, not available.

When Should Plasma CRP Be Sampled After Ischemic Stroke?

In patients with acute ischemic stroke, plasma CRP concentrations are elevated early and remain elevated above control values at 3 months after the index stroke.²⁰ The available

data suggest the usefulness of a sample taken within 12 to 24 hours after stroke onset,^{14,15,19} although one of these studies has found plasma CRP concentrations at discharge to be better predictors of the mid-term to long-term prognosis than those at admission, whereas the peak

measurement in the first week was particularly valuable in relation to infarct volume and clinical outcome.²⁰ The CRP concentration is persistently increased after stroke,²⁰ but to what extent the elevation reflects the inflammatory response to stroke as opposed to the underlying atherosclerosis has not been established. It is possible that discharge concentrations more closely reflect the baseline inflammatory status of the patients and thus their intrinsic risk caused by inflammatory activity. A case can be made for assessment of the CRP concentration at admission to the hospital, at discharge when possible, at 1 to 3 months, and then at further intervals because it is likely that the highest risk of future events is present in patients with persistently elevated CRP.¹⁰ However, mortality is significant in patients who have increased CRP in the first week,⁸² and we would recommend that the optimum time for assessment of the CRP concentration be determined definitively in a well-defined, prospective study. Further prospective studies of the optimal timing of CRP measurement for use as a prognostic marker after ischemic stroke are warranted.

Pitfalls of CRP Measurement

Assays with sufficient sensitivity to measure the (log) normal range of plasma CRP have not been widely used until recently. This was not because of any particular technical difficulty, but rather because modest deviations were not considered useful. Increasing use of what has become known as the hsCRP assay has identified that plasma CRP concentration is influenced chronically by a large number of disease states and physiological factors, including heart failure,^{92,93} cardiac arrhythmias,^{94–96} renal insufficiency,^{97,98} diabetes mellitus,^{99–108} obstructive sleep apnea,^{109,110} arterial hypertension,^{108,111–113} obesity,^{100,105,114–118} insulin resistance syndrome,^{117,119} metabolic syndrome,^{53,119–121} estrogen use,^{122–125} frequent physical activity,^{126–129} moderate alcohol consumption,^{130–132} high-protein diet,¹¹⁶ and depressive symptoms.^{133–135} Plasma CRP concentration has also been shown to be influenced by genetic factors,^{136–139} and modest CRP elevation may be a marker of biologic aging¹⁴⁰ and decline of cognitive function,^{141,142} in addition to being a predictive marker of disability, poor prognosis, and mortality in the elderly.^{143,144} It is additionally associated with other CVD risk factors, such as periodontal disease^{145–147} and smoking,^{116,148} which are more probably related to local, nonarterial inflammation.

Specificity of CRP for inflammation is not absolutely clear, because modest CRP elevations may not reflect an easily identifiable inflammatory state. An example of this might include obesity, which has been shown to be associated with increased expression of inflammation-associated cytokines in adipose tissue and plasma, but in the absence of a classical tissue inflammatory response.^{149–151} Induction of classical inflammatory markers, such as CRP, may therefore be a common factor in a wide variety of disease states, extending well beyond the original clinical role for CRP assays. Epidemiological studies must take a large number of potential confounders and interactions into account. At least 2 fundamental issues must be addressed. Does elevated CRP provide a biomarker for inflammatory activity that is a useful target of treatment (whether by lifestyle interventions, such as smok-

ing cessation or weight reduction, or by specific drug therapy such as statins)? Does specific reduction of CRP (or other inflammatory mediators) provide benefit in cerebrovascular disease risk or prognosis?

In using CRP for assessment of cerebrovascular risk, it is essential to clearly establish whether high CRP concentrations are the result of concomitant pathologies. When measured with high-sensitivity assays, the population distribution of CRP has generally been consistent across sex and ethnic groups, and values of 0.3, 0.6, 1.5, 3.5, and 6.6 mg/L have been reported as estimates of the 10th, 25th, 50th, 75th, and 90th percentile cut-points for middle-aged Americans.⁷² Similar results are also found in different European, North American, and Japanese cohorts,^{152–158} although differences between men and women, influenced by oral contraceptive usage, are also reported.¹⁵⁹ Unfortunately, data on CRP concentrations in populations from developing countries are sparse, so any generalization in these populations should be made with caution because a different prevalence of risk factors, concurrent subclinical infections, and genetic differences could affect CRP concentration. However, in one study, race and ethnicity did not appear to modify the association between hsCRP and stroke.⁷⁵ Further studies in this area are mandatory before extending the evaluation of CRP concentrations to the prediction of cerebrovascular risk in developing countries. The within-subject variability in CRP concentrations in apparently healthy individuals is 4- to 6-times greater than that for total cholesterol, with interquartile values ranging between 150% and 250% of the median and an estimate of the composite coefficient of variation of $\approx 120\%$.^{160–162} However, the scale used is important and plasma CRP is approximately log-normally distributed.¹⁶³ The CRP mean within-subject variability is $\approx 30\%$ for several groups and periods.¹⁶¹ This implies that it would not be unusual for a subsequent CRP measurement to be $\approx 60\%$ higher or lower than the initial reading. However, the range of CRP measurements is considerable and it has been suggested that CRP has the same degree of measurement stability as total cholesterol.^{156,158,163,164} This conclusion was based on the Ridker-Rifai quartile model¹⁶³ classifying CRP into 4 arbitrarily defined categories of unequal sizes and cholesterol into quartiles of equal size. This is consistent with the log-normal distribution of CRP. Approximately 60% of repeated measurements were found to fall into the same category for CRP or the same quartile for cholesterol.

A large number of CRP assays are now available commercially. Because measurements of CRP concentration were traditionally used to diagnose and monitor more severe acute and chronic inflammation, CRP assays conventionally had cutoff points (typically 3 to 6 mg/L) and were not required to be highly sensitive. The hsCRP assays have been developed with detection limits of ≈ 0.1 mg/L. Variability between these newer assays could, however, result in variation in the classification of patients using population-based CRP cut-points,¹⁶⁵ and further work is necessary to ensure standardization. With these issues in mind, work has recently been conducted to achieve standardization of hsCRP immunoassays with respect to both reference materials and assay methodology.¹⁶⁶

Analytical variation and assay imprecision can produce clinically significant variation in risk estimates that only multiple measurements may reduce.¹⁶⁴ Provided that the appropriate scale is used, 2 sequential samples have been found to be appropriate for clinical use,¹⁶³ although the need for this can be reduced by a strategy whereby this is performed only when the initial value is above a concentration that indicates a 100% sensitivity for detecting unreliable values.¹⁵⁹ This may be different in men and women, especially in women using oral contraceptives. Women using HRT also have higher concentrations of CRP,^{4,72,157,167,168} and risk estimates for such women may need to be calibrated downward. An additional complication is that plasma CRP concentration may be affected by genetic factors, including polymorphisms in the CRP gene and/or other factors influencing CRP induction such as polymorphisms in the IL-6 gene promoter region.^{169,170} However, if CRP is simply a marker, reflecting inflammatory state, any factor that alters the relationship between its concentration and inflammation

may distort interpretation. It may therefore become important to interpret any CRP concentration in the context of an individual's genotype.

Is the Measurement of Plasma CRP Justified in the Routine Clinical Assessment of Stroke Risk in Primary or Secondary Prevention?

CRP might be a good candidate, but appropriate clinical cut-points for CRP in the setting of acute cerebral ischemia have not yet been established, nor has the timing of CRP evaluation in relation to the onset of ischemia been determined. The predictive accuracy of isolated CRP measurement is limited regarding traditional risk factors.¹⁷¹ An elevated CRP in this setting is associated with increased mid-term to long-term risk,^{11,13-15,17-19,79,80,82} and thus additional evaluation modalities may be warranted.

Data from large randomized, controlled trials showing that interventions aimed specifically at reducing CRP concentrations will lower the risk of subsequent CVD events in the

TABLE 3. Recommendations for CRP Use in Cerebrovascular Disease

Procedure Should Be Performed (Class I)	Conflicting Evidence/Opinion: Weight in Favor of Usefulness/Efficacy (Class IIa)	Conflicting Evidence/Opinion: Usefulness/Efficacy Less Well-Established (Class IIb)	Procedure Should Not Be Performed (Class III)
1. Risk factor assessment with attention to optimizing primary and secondary preventive measures for cerebrovascular disease should remain the essential objective of clinicians. In most cases, assessment of standard risk factors should suffice to determine most patients who are at greatest risk and guide appropriate medical and lifestyle modifications (class I, level of evidence A)	2. Elevated plasma CRP is an independent marker of ischemic stroke risk (class IIa, level of evidence B)	3. In patients with ischemic stroke, elevated CRP is an independent marker of prognosis for recurrent cardiovascular events, including vascular death, MI, and disease or acute coronary syndromes (class IIb, level of evidence B)	5. There is insufficient evidence at present to alter secondary preventative therapy for cerebrovascular disease on the basis of plasma CRP concentrations; application of secondary prevention measures should not be dependent on plasma CRP concentrations (class III, level of evidence C)
		4. In clinical practice settings, there is insufficient evidence to justify the routine use of plasma CRP in either primary or secondary risk stratification for cerebrovascular disease alone (class IIb, level of evidence B)	6. Application of management guidelines for ischemic stroke should not be dependent on plasma CRP concentrations (class III, level of evidence C)

CRP indicates C-reactive protein; MI, myocardial infarction.

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primary or secondary prevention setting are also lacking. Without this information, use of CRP assay either acutely or as a screening modality will be limited. Because the occurrence of an ischemic cerebrovascular event itself defines an individual as being at high risk, aggressive secondary preventative therapy is justified in the majority of patients, and it is not yet certain how CRP concentration might be used to modify this approach. Clinical use of a CRP assay in secondary prevention situations cannot be recommended at the present time until multicenter, carefully controlled studies have been undertaken in ischemic stroke patients.

Although CRP is a promising independent predictor of primary cerebrovascular events, the current data are not as clear as for CVD (Table 3). For the moment, the extensive use of plasma CRP testing on the basis of cerebrovascular risk alone should be discouraged in routine clinical practice, except when combined vascular risk is being assessed. However, distinct risk factors, such as lack of association between cholesterol and stroke, indicate the value of determining specific association with cerebrovascular disease risk.

What to Do When CRP Concentrations Are Elevated

The management of individuals with elevated plasma CRP identified as being at risk for vascular events remains unclear. There is currently no specific therapy to reduce plasma CRP concentration and to improve cerebrovascular risk or to improve outcome after ischemic stroke in placebo-controlled trials. Observational data suggest that statins⁷⁹ and angiotensin-converting enzyme inhibitors¹⁷² are probably more effective in the presence of high CRP concentrations and that the efficacy of antiplatelet therapy¹⁶ in secondary prevention appears to be directly related to the levels of inflammatory markers. These observations suggest that individuals with higher CRP concentrations might benefit from more aggressive medical therapy. The use of biochemical markers for guiding therapy might not be a controversial issue in the future, and there is no doubt that CRP possesses suitable characteristics for this purpose. However, additional well-designed epidemiological studies are needed to validate these findings. Whereas high CRP may be of value in targeting aggressive treatment in patients with risk factors but no overt clinical manifestations of cerebrovascular disease—ie, primary prevention—a case cannot be made at present for changing secondary prevention. Several pharmacological agents proven to reduce vascular risk influence CRP concentrations. Of these, the statin drugs are the most important, and studies with pravastatin, lovastatin, cerivastatin, simvastatin, atorvastatin, and rosuvastatin have all shown that, on average, median CRP concentrations decline by 15% to 40% as early as 6 weeks after initiation of therapy.¹⁷³ Although the data for other lipid-lowering agents are less robust, fibrates appear to act in a similar manner,^{174,175} and niacin and gemfibrozil have also been reported to reduce CRP concentration.¹⁷⁶

Whether lowering CRP concentrations represents a useful pharmacological goal in itself is unclear. Evidence from animal studies in myocardial infarction and ischemic stroke has shown that CRP exacerbates ischemic injury in the acute phase, through complement binding,^{42,177–180} but the extent to

which this mechanism is pathophysiologically relevant in the chronic inflammatory response to atherosclerosis is uncertain.

Statins lowered CRP independent of cholesterol parameters in the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TEXCAPS)¹⁸¹ and appeared to be more effective in reducing CV endpoints in primary or secondary prevention studies of lipid-lowering in individuals with higher CRP concentrations.^{181,182} It remains unclear whether CRP is simply a marker of treatment effect on systemic atherosclerosis, or represents a therapeutic target. Results from the Heart Protection Study Collaborative Group indicated that efficacy of statins for protection of individuals at high risk from either CV or cerebrovascular events was not greater in those with raised cholesterol, suggesting the likelihood of an alternate protective action.¹⁸³ Because cerebrovascular endpoints have not been studied as a primary goal of trials to date, further trials in primary and secondary prevention are required. A large randomized clinical trial (JUPITER) has already been initiated to evaluate the effects of statin (rosuvastatin) therapy in primary prevention of stroke as part of a combined vascular end-point in individuals with LDL cholesterol concentration <3.36 mmol/L who are judged to be at high vascular risk on the basis of a CRP concentration ≥ 2 mg/L.¹⁸⁴

Whereas strategies involving CRP screening for the primary and secondary prevention of CHD among middle-aged subjects have apparently proven to be relatively cost-effective and, in some cases, cost-saving,^{185–187} consistent data in stroke and elderly patients are scant.¹⁸⁸ Additional well-designed epidemiological studies are needed to define the potential role of CRP-based screening in primary prevention of stroke. It is important that these issues be fully resolved in such prospective studies before CRP screening becomes accepted practice. It is important that future studies specifically address stroke as a primary end-point, because ischemic stroke differs from CHD in terms of physiopathology and probably in response to pharmacotherapy (eg, statins, aspirin, and clopidogrel are more effective in CHD, whereas reduction of BP is more effective in stroke).¹⁸⁹ In addition, stroke studies should ensure that stroke events are characterized as accurately as possible, because treatment effects may differ significantly, for example, between small-vessel disease and large-vessel atherosclerosis.^{190–192} Therefore, at the current time evidence is not available to propose the use of CRP concentration as a guide of statin therapy in cerebrovascular disease prevention alone, but common factors in cerebrovascular disease and CVD suggest its value for reducing combined risk.

Future Perspectives

The pathophysiological role of CRP in atherothrombosis and its ischemic complications may have several implications for future research, including the exploration of therapeutic strategies in CVDs: (1) CRP, or other inflammatory markers regulating its synthesis, such as IL-1, tumor necrosis factor- α , or IL-6, may become targets for intervention, eg, by inhibiting hepatic biosynthesis, blocking or modulating CRP actions, or those of the upstream cytokines; (2) directly targeting cytokine or CRP-mediated effects may influence

progression of atherosclerosis, plaque stability, or reduce ischemic tissue damage; however, the primary cause for the accumulation and activation of inflammatory cells in the arterial subintimal space and the subsequent expression of pro-inflammatory cytokines and other mediators which play an important role in plaque progression and ultimately contribute to plaque destabilization and rupture, still remains largely unclear; and (3) the correlation of circulating post-stroke CRP concentrations with stroke severity,^{14,15,19,82} extent of ischemic lesion,^{14,15,19,82} and the prognostic significance of these associations^{14,15,19,82} may merely reflect CRP being a marker of tissue injury, but CRP might also contribute to the pathogenesis of ischemic stroke and tissue injury. Novel drugs that specifically block CRP binding and its proinflammatory effects in vivo could provide clear evidence for this concept.^{49,50} Such drugs would be a powerful tool for determining whether increased CRP production does participate in the pathogenesis of atherosclerosis and its ischemic complications.

APPENDIX. American College of Cardiology/American Heart Association Classification of Recommendations and Levels of Evidence²⁶

Classification of Recommendations

Class I: Conditions for which there is evidence and/or general agreement that a given procedure is useful and effective

Class II: Conditions for which there is conflicting evidence and/or divergence of opinion about the usefulness/efficacy of a procedure or treatment

Class IIa: Weight of evidence/opinion is in favor of usefulness/efficacy

Class IIb: Usefulness/efficacy is less well-established by evidence/opinion

Class III: Conditions for which there is evidence and/or general agreement that the procedure/treatment is not useful/effective and in some cases may be harmful

Levels of Evidence

Level of Evidence A: Data derived from multiple randomized clinical trials

Level of Evidence B: Data derived from a single randomized trial or nonrandomized studies

Level of Evidence C: Consensus opinion of experts

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Evaluation of C-Reactive Protein Measurement for Assessing the Risk and Prognosis in Ischemic Stroke: A Statement for Health Care Professionals From the CRP Pooling Project Members

Mario Di Napoli, Markus Schwaninger, Roberto Cappelli, Elena Ceccarelli, Giacinto Di Gianfilippo, Cristina Donati, Hedley C.A. Emsley, Sandro Forconi, Stephen J. Hopkins, Luca Masotti, Keith W. Muir, Anna Paciucci, Francesca Papa, Sabina Roncacci, Dirk Sander, Kerstin Sander, Craig J. Smith, Alessandro Stefanini and Daniela Weber

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