Stroke

CLINICAL AND POPULATION SCIENCES

Rationale, Design, and Implementation of Intensive Risk Factor Treatment in the CREST2 Trial

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BACKGROUND AND PURPOSE: The CREST2 trial (Carotid Revascularization and Medical Management for Asymptomatic Carotid Stenosis) is comparing intensive medical management (IMM) alone to IMM plus revascularization with carotid endarterectomy or transfemoral carotid artery stenting for preventing stroke or death within 44 days after randomization or ipsilateral ischemic stroke thereafter. There are extensive clinical trial data on outcomes after revascularization of asymptomatic carotid stenosis, but not for IMM. As such, the experimental treatment in CREST2 is IMM, which is described in this article.

METHODS: IMM consists of aspirin 325 mg/day and intensive risk factor management, primarily targeting systolic blood pressure <130 mm Hg (initially systolic blood pressure <140 mm Hg) and LDL (low-density lipoprotein) cholesterol <70 mg/dL. Secondary risk factor targets focus on tobacco smoking, non-HDL (high-density lipoprotein), HbA1c (hemoglobin A1c), physical activity, and weight. Risk factor management is performed by site personnel and a lifestyle coaching program delivered by telephone. We report interim risk factor data on 1618 patients at baseline and last follow-up through 24 months.

RESULTS: The mean baseline LDL of 80.5 mg/dL improved to 66.7 mg/dL. The mean baseline systolic blood pressure of 139.7 mm Hg improved to 130.3 mm Hg. The proportion of patients in-target improved from 43% to 61% for systolic blood pressure <130 mm Hg and from 45% to 67% for LDL<70 mg/dL (both changes $P<0.001$).

CONCLUSIONS: The rigorous multimodal approach to intensive stroke risk factor management in CREST2 has resulted in significant improvements in risk factor control that will enable a comparison of cutting-edge medical care to revascularization in patients with asymptomatic carotid stenosis.

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Key Words: blood pressure ■ carotid stenosis ■ endarterectomy, carotid ■ risk factors ■ stent

Carotid stenosis causes 7% to 18% of ischemic strokes in the United States.[1,2] Prior randomized trials comparing medical therapy to carotid endarterectomy for stroke prevention were conducted over 15 years ago. In the ACAS (Asymptomatic Carotid Atherosclerosis Study)[3] and ACST (Asymptomatic Carotid Surgery Trial)[4] trials, the primary end point rates in the medical groups were ≈2% per year. However, observational data from 2002 to 2009 of patients with ≥50% asymptomatic carotid stenosis reported an ipsilateral stroke rate of 0.34% (95% CI, 0.01–1.87) per year.[5] This apparent improvement in vascular event rates has been attributed to secular improvements in risk factor control. In ACAS, control

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Nonstandard Abbreviations and Acronyms

ACAS	Asymptomatic Carotid Atherosclerosis Study
ACST	Asymptomatic Carotid Surgery Trial
CREST	The Carotid Revascularization Endarterectomy versus Stenting Trial
CREST2	Carotid Revascularization and Medical Management for Asymptomatic Carotid Stenosis
IMM	intensive medical management
MMC	CREST2 Medical Management Core
PACE	Physician-Based Assessment and Counseling for Exercise
SAMMPRIS	Stenting versus Aggressive Medical Therapy for Intracranial Arterial Stenosis
SBP	systolic blood pressure

of vascular risk factors was not monitored. In ACST, from the early 1990s to 2007, the percentage of patients taking antihypertensive therapy increased from 53% to 88% and use of lipid-lowering drugs increased from 10% to 81%, with lower stroke rates among those on lipid-lowering therapy.[6]

Similarly, in the CREST (Carotid Revascularization Endarterectomy Versus Stenting Trial), which included 1181 patients with asymptomatic carotid stenosis, those enrolled in later years (2005–2008) had better risk factor control at baseline than those enrolled earlier in the enrollment period (2000–2004).[7] This improved risk factor control may be reflected in the low stroke rate beyond the periprocedural period among asymptomatic patients who underwent transfemoral carotid artery stenting and carotid endarterectomy (2.5% and 2.7% over 5 years, respectively).[8]

Without specific risk factor protocols in CREST, over the 4-year follow-up of asymptomatic patients, the mean LDL (low-density lipoprotein) concentration improved by only 7.8 mg/dL and the mean systolic blood pressure (SBP) improved by 5 mm Hg.[7] In contrast to CREST, the SAMMPRIS trial (Stenting Versus Aggressive Medical Therapy for Intracranial Arterial Stenosis) used multimodal intensive risk factor management with central oversight.[9] SAMMPRIS achieved significant improvements in risk factor control from baseline to 1 year, including a mean decrease in LDL of 30 mg/dL and SBP of 15 mm Hg.[10] Because of this success and the effect of risk factor control on events rates in other trials,[11–14] a strategy similar to SAMMPRIS was adopted for the CREST2 trials (Carotid Revascularization and Medical Management for Asymptomatic Carotid Stenosis). The purpose of this article is to describe the rationale, design, and successful implementation of a program of intensive medical management (IMM) of vascular risk factors in CREST2.

METHODS AND DESIGN

The design of the ongoing CREST2 trial has been published,[15] and data will be available at the end of the trial in accordance with the NIH data sharing policy. The institutional review board of each participating center or the Central Institutional Review Board for StrokeNet sites approved the protocol and all patients gave informed consent. Briefly, CREST2 is 2 parallel randomized trials of (1) IMM alone versus IMM plus revascularization with carotid endarterectomy and (2) IMM alone versus IMM plus transfemoral carotid artery stenting. Patients with asymptomatic ≥70% atherosclerotic carotid stenosis are enrolled at up to 150 centers based upon eligibility criteria for carotid endarterectomy or carotid artery stenting. The primary end point is stroke or death within 44 days after randomization or ipsilateral ischemic stroke thereafter at 4 years.

Overview of IMM

IMM consists of aspirin 325 mg/d during the follow-up period (plus clopidogrel 75 mg/day for 90 days following carotid artery stenting) and intensive vascular risk factor management, primarily targeting SBP <130 mm Hg and LDL <70 mg/dL. The CREST2 risk factors targets are shown in Table 1. The rationale for each target, as well as target revisions during the study, are detailed in Appendix I in the Data Supplement. Hypertension and hyperlipidemia were selected as primary risk factor targets because they have the highest population-attributable risk for carotid stenosis.[16] Because they also contribute to carotid stenosis, diabetes mellitus,[17] smoking,[16] physical inactivity,[18] and obesity[19,20] were selected as secondary risk factor targets. Risk factor management is performed by site Medical Management Physicians and research coordinators, assisted by a telephonic lifestyle modification program.

The design of risk factor management protocols in CREST2 was largely based on successful strategies employed in prior trials.[9,21] These strategies include providing medication titration algorithms for hypertension and hyperlipidemia, providing free study medications for patients as needed, standardizing measurement of risk factors, standardizing IMM training of site personnel, and centralizing oversight of risk factor control. The CREST2 Medical Management Core (MMC) oversees implementation and consists of a director, project manager, research assistant, and members of the Risk Factor Management Committee, providing access to lipid and hypertension experts for advice on specific cases.

Medication Titration Algorithms

CREST2 employs algorithms (Figures 1 and 2) that use guideline-based medications targeting risk factors, such as atorvastatin for LDL and an angiotensin converting enzyme inhibitor or thiazide diuretic for SBP, which are started as needed at baseline and titrated at each subsequent visit until the target is achieved. Patients undergo extra blood pressure follow-up visits every 30 days until SBP is in-target. Repeat lipid panels are recommended 30 days after starting or changing a lipid-lowering medication to assess response. If the Medical Management Physician is unable

Table 1. CREST2 Risk Factor Targets

Risk Factor	Goal	Measurement
Primary risk factor		
LDL	<70 mg/dL*	Local clinical laboratory
SBP	<130 mm Hg†	Using standardized device provided to site
Secondary risk factor		
Non-HDLc	<100 mg/dL	Local clinical laboratory
HbA1c	<7.0%‡	Local clinical laboratory
Smoking	Cessation	Self reported (PACE score§)
Weight management	For initial BMI of 25–27 kg/m^2: target BMI <25 kg/m^2	Weight at each visit
	For initial BMI>27 kg/m^2: target 10% weight loss	Height at baseline
Physical activity	≥30 min of moderate exercise ≥3× per wk	Self reported (PACE score§)

BMI indicates body mass index; CREST2, Carotid Revascularization and Medical Management for Asymptomatic Carotid Stenosis; HbA1C, hemoglobin A1c; HDLc, high-density lipoprotein cholesterol; LDL, low-density lipoprotein; PACE, Physician-Based Assessment and Counseling for Exercise; and SBP, systolic blood pressure.

*Measured at baseline and annually. Additional measurements required at 44 d and 4 mo if not in-target and after starting or adjusting a lipid-lowering medication.

†Changed from <140 in 2018. Measured at baseline and each study visit. Additional measurements required at 30-d intervals if out-of-target.

‡Measured in diabetic patients only every 6 mo or sooner if needed for standard-of-care clinical purposes.

§PACE questionnaire is performed for smoking and exercise. Smoking in-target is defined as PACE of 1, 5, or 6. Physical activity in-target is defined as PACE ≥4.

to lower the patient's LDL or SBP to achieve the treatment target by following the trial algorithms, the MMC provides individually tailored patient assistance. Patients who the MMC deems to be incapable of achieving risk factor targets due to medication intolerance, noncompliance, or other factors may be designated as risk factor target failure and are not required to return for medication titration, although they adhere to standardized scheduled follow-up visits to assess for trial end points.

Study Medications

Medications given to achieve LDL and SBP targets are provided to patients free of charge if they lack prescription insurance. Selected medications are provided via a national retail pharmacy chain and billed directly to the study. The antihypertensive medications include one generic drug from almost every drug category (see Figure 1B).

Atorvastatin was selected for lipid-lowering due to efficacy and cost. Patients who are not at LDL target at baseline are encouraged to start or switch to atorvastatin. Additional medications, such as ezetimibe and PCSK9 (proprotein convertase subtilisin/kexin type 9) inhibitors, are used to achieve LDL targets in patients on maximum tolerated doses of statins.[22] PCSK9 inhibitors have demonstrated efficacy in the reduction of LDL[23] and major cardiovascular events,[24] but high costs have limited access. Therefore, alirocumab is provided free of charge by Sanofi-Aventis US LLC and Regeneron Pharmaceuticals, Inc, to qualifying patients who are not achieving the LDL target on the maximum tolerated dose of statin. The donated alirocumab program was launched in April 2018 and delivers Medical Management Physician-prescribed alirocumab via a mail-order pharmacy directly to the patient's home.

Standardizing Measurement of Primary Risk Factor Levels

Accurate measurement of the primary risk factors is required for reliable correlations between risk factor control and clinical outcomes at the end of CREST2. Blood pressure monitoring devices vary in their accuracy,[25] and guidelines recommend use of well-calibrated and validated automated devices.[22] Therefore, all sites are required to use the same make and model (HEM-705CP Omron; Kyoto, Japan) of a highly rated blood pressure monitoring device[26] (provided by CREST2). At each visit, 3 consecutive BP measurements are done 1 to 2 minutes apart and averaged to determine the BP for that visit. To identify patients with orthostatic hypotension, standing BP is checked at baseline and the 12-month visit. At all visits, the patient is asked if he/she has any orthostatic symptoms, and if present, standing BP is checked. Standing BP is also checked if the patient had a standing SBP drop of >15 mm Hg at last visit. To reduce variability in readings, coordinators are trained on how to obtain a resting, seated brachial artery blood pressure measurement in a required 10-minute training module.

LDL values are standardized by the requirement to be performed at Clinical Laboratory Improvement Amendments (CLIA)[27]–certified laboratories and may be calculated from fasting or nonfasting samples.[28] However, if the triglyceride level is >400 mg/dL, the LDL cannot be calculated, and a direct measurement of LDL is required.

Lifestyle Modification Program

Remote wellness and lifestyle modification programs have reported improvement in multiple vascular risk factors in a variety of populations.[29] In the SAMMPRIS trial, which employed a telephonic lifestyle modification program, good participation in the program was associated with improved risk factor target achievement.[30] Hence, a lifestyle modification program was incorporated in CREST2. INTERVENT (Savannah, Georgia) was selected because it is internationally available and is delivered with telephonic counseling. INTERVENT provides lifestyle counseling with 2 calls per month for the first 3 months, 1 call per month for the rest of the first year, and 2 calls per year in years 2 to 4. Details on INTERVENT interaction between the patients, sites, and MMC are provided in Appendix II in the Data Supplement.

Standardized IMM Training

Detailed and ongoing training on the IMM protocols is provided at the annual Principal Investigators' and Coordinators' Meetings.

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Due to the addition of sites and existing site personnel turnover, interactive eLearning modules were developed to deliver ongoing IMM training and are required of all Medical Management Physicians and coordinators before site initiation. Study newsletters and conference calls of principal investigators, Medical Management Physicians, and coordinators are also used to provide updated training. An IMM Manual of Operations (updated regularly) and other documents related to risk factor control (eg, guideline statements, medication titration algorithms, etc) are available on the CREST2 website (www.crest2trial.org).

Central Monitoring of Risk Factor Performance

Overall site risk factor performance is monitored by the MMC using (1) weekly reports of sites' risk factor target performance, (2) reports detailing protocol implementation (eg, list of patients with missed BP revisits, patients with elevated LDL who are not on a maximum dose of statin), and (3) individual patient reports (which include patient's risk factors, laboratory tests, and medication log). Sites with poor compliance with IMM protocols (eg, delay in titrating medications, failure to obtain risk factor values) are identified and additional training of site personnel is implemented, as needed. Automated email reminders to the site for upcoming expected BP revisits or reassessments of LDL are other tools for compliance.

The MMC provides recommendations for individual patients at the site's request or for patients who are persistently out-of-target. These recommendations are provided by members of the Risk Factor Management Committee who have specific expertise (eg, BP or lipid management). All patient-specific communications between the MMC and sites are logged to ensure consistency and follow-up.

The Risk Factor Management Committee also meets bi-annually to evaluate the success of IMM and to recommend updates to protocols if justified by new research or guidelines.

Statistical Analyses

Risk factor values for each visit are used to determine target status (in or out). For all follow-up visits if a value is missing, the last nonmissing observed value is used to determine target

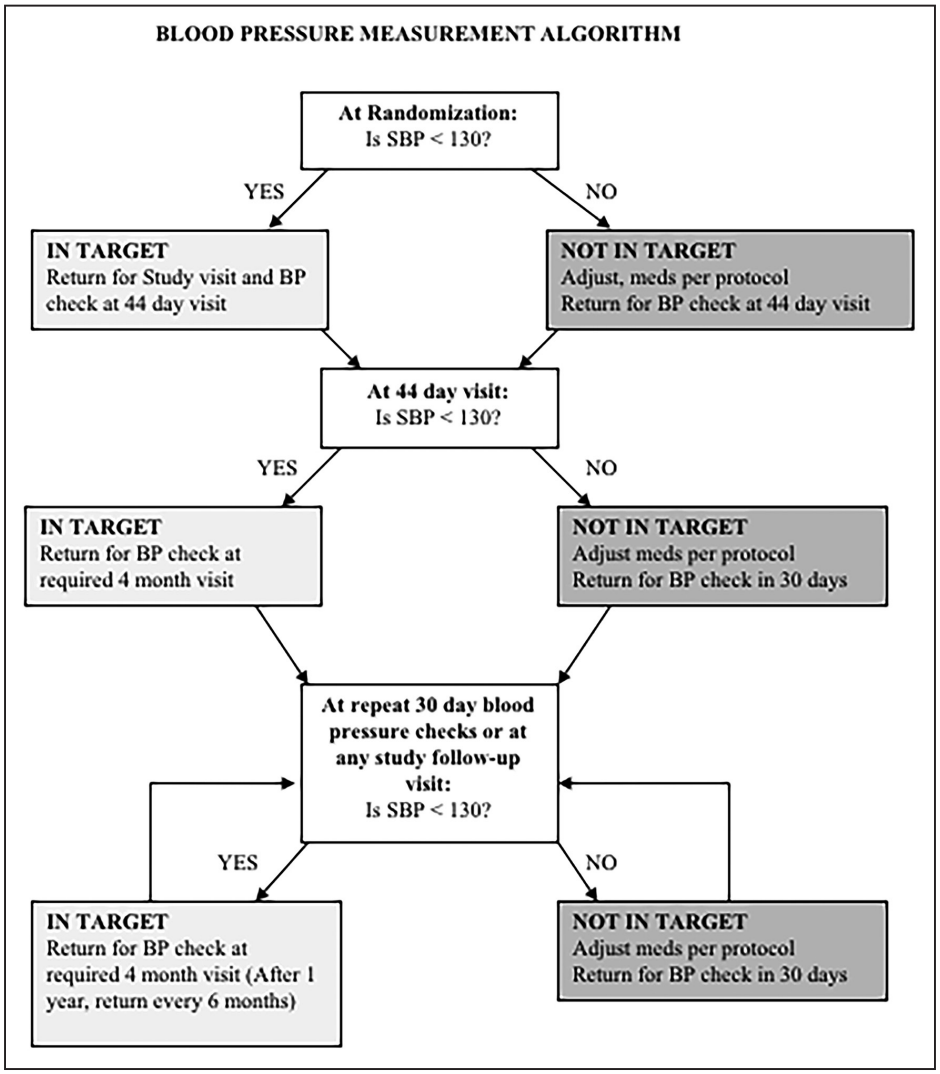

Figure 1. Management of blood pressure.
A, Blood pressure (BP) measurement algorithm; (**B**) hypertension treatment algorithm. ACEI indicates angiotensin-converting enzyme inhibitor; Afib, atrial fibrillation; ARB, angiotensin receptor blocker; CAD, coronary artery disease; CCB, calcium channel blocker; CHF, congestive heart failure; CKD, chronic kidney disease; CREST2, Carotid Revascularization and Medical Management for Asymptomatic Carotid Stenosis; DHP, dihydropyridine; GFR, glomerular filtration rate; HCTZ, hydrochlorothiazide; HR, heart rate; and SBP systolic BP. (*Continued*)

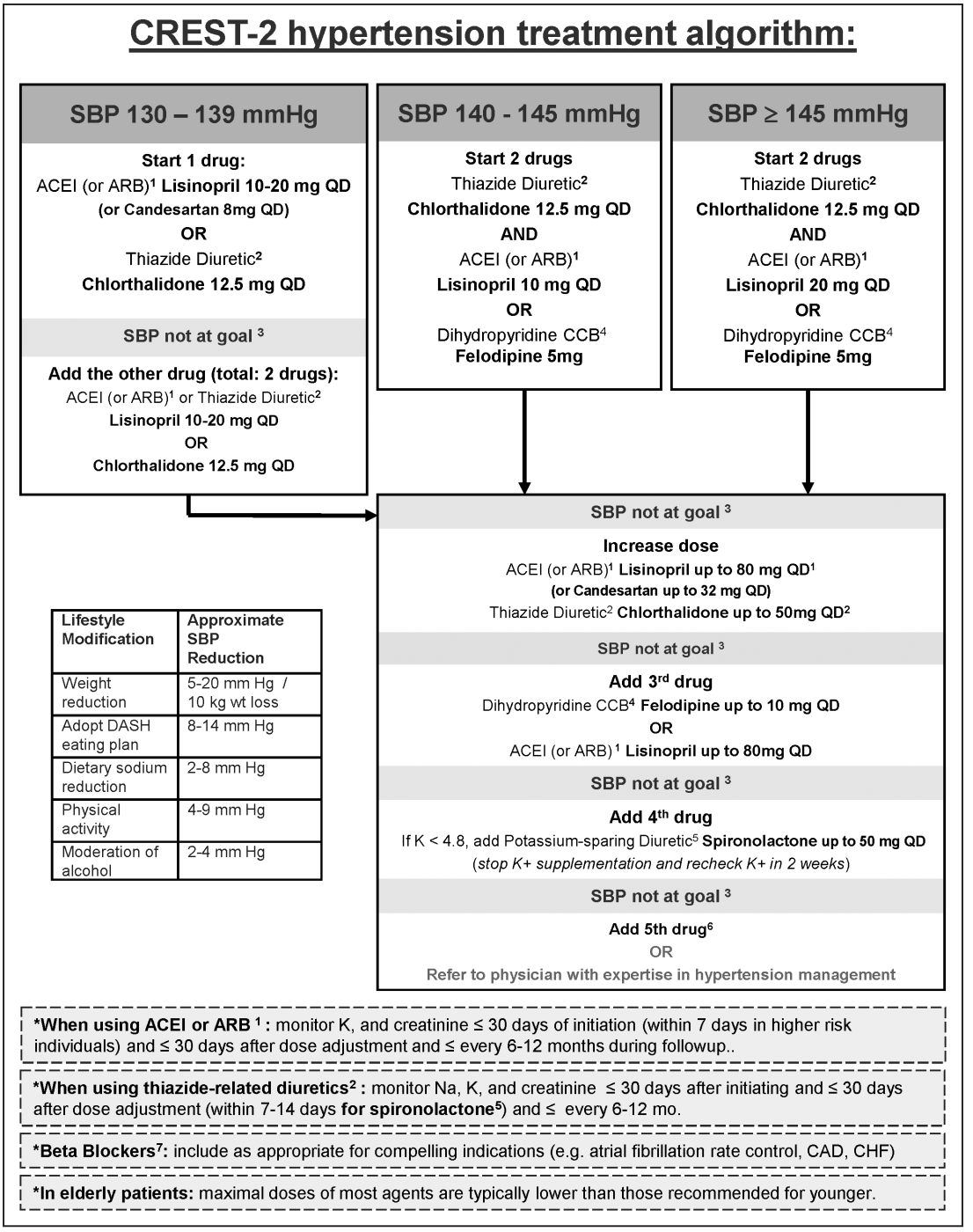

Figure 1 Continued.

status (ie, the target status remains the same until a new value is entered). If a baseline value is missing, the target status is missing. The LDL or SBP target is waived for a visit if the patient is designated risk factor target failure or if the patient has orthostatic hypotension (defined as a standing drop in SBP ≥15 mm Hg, with or without orthostatic symptoms) because a medication change is not required.

For these risk factor control analyses, paired comparisons between proportion in-target at baseline and last follow-up were done using McNemars test. Backward Logistic regression was conducted to assess factors associated with being in-target at last follow-up for both LDL and SBP. Factors assessed in univariate analysis were age, sex, ethnicity, race, alcohol use, history of sleep apnea, depression, and diabetes mellitus, as well as whether patients were in-target for body mass index, physical activity, and smoking at baseline.

RESULTS

CREST2 enrollment began in 2014 and is expected to continue through 2022. Interim risk factor data from

Algorithm is based on hypertension guidelines and CREST-2 formulary.

1. **Angiotensin converting enzyme inhibitors (ACEI):** Initiate treatment with ACEI (or ARB) in non-black patients and in those with CKD. **Lisinopril** is the ACEI in the CREST2 formulary. Many other ACEI are available (enalapril, captopril and benazepril are also generic and very affordable). Start lisinopril at 10-20 mg/day and increase stepwise to maximum of 80 mg/day. Some experts prefer to use ACEI twice a day when in high doses (remember compliance decreases sharply if drugs are used more than daily). Can substitute **Candesartan** (the angiotensin receptor blocker (ARB) in the CREST2 formulary) ONLY if known intolerance to ACEI. Start candesartan at 8mg/day; increase up to 32 mg per day in daily doses. **When using ACEI or ARB, monitor K+ and creatinine ≤ 30 days after initiating (within 7 days in higher risk individuals - GFR <30, bilat renal artery stenosis, CHF, volume depletion, NSAID use), and ≤ 30 days after dose adjustment and at ≤ every 6-12 month intervals. Do not use ACEI and ARB in combination.**

2. **Thiazide diuretic**: Initiate treatment with thiazide in black patients. In patients with normal kidney function start **chlorthalidone** 12.5 mg per day or hydrochlorothiazide (HCTZ) 12.5 mg twice daily (HCTZ is approximately 50% less potent and much shorter acting than chlorthalidone). Increase doses of either to 25 mg as needed. In some cases higher doses can be used (rarely >50mg chlorthalidone/day). Thiazide diuretics may induce hyponatremia, particularly in elderly patients within 1-2 weeks of initiation or change in dose and this may be worsened by concurrent use of NSAIDs. In patients with history of hyponatremia and in those with CKD (GFR <30), use loop diuretics instead. **Always use furosemide at least twice a day.** A loop diuretic dosed once daily is torsemide (start at 10-20 mg/day). **When using diuretics, monitor Na+, K+ and creatinine ≤ 30 days after initiating and dose adjustment and ≤ every 6-12 months.**

3. **Blood pressure not at goal**: If compliance is good, adjust doses of medications **every 30 days**. In some cases changes can be made more often (every 2 weeks). *It is better to* ***start drugs in moderate doses*** *(1 or 2 agents)* ***and wait*** *than start very low and make frequent adjustments (because it usually takes a minimum of 2 weeks to see the full effect of most drugs).* **If compliance is questioned, counsel patient on importance of taking BP meds as directed and recheck BP in 2 weeks**.

4. **DHP Calcium channel blockers (CCB):** Use as second line with diuretic in black patients, otherwise third line. **Felodipine** is the drug in the CREST2 formulary. Start in doses of 5 mg per day; increase to maximum 10 mg per day. Other popular drugs in this class are amlodipine (Norvasc) and nifedipine (Adalat). These are effective vasodilators and are best combined with long acting diuretics and ACEI (or ARB) to diminish the peripheral edema common to these agents. ***NEVER use short acting nifedipine***.

5. **Potassium-sparing Diuretic:** **Spironolactone** is an aldosterone antagonist that provides significant additional BP reduction in patients with resistant hypertension with and without primary hyperaldosteronism (*AJH 2003; 16:920-930).* Should not be started in patients with K+ > 4.8; use with caution with impaired kidney function. May offset hypokalemic effects of thiazide diuretics. **Monitor Na+, K+ and creatinine within 7-14 days after initiating and ≤ 30 days after dose adjustment and ≤ every 6-12 months. Stop potassium supplements when starting K-sparing drugs including ACEI/ARBs.**

6. **Add 5th Drug/Refer to hypertension specialist.** Adding more agents may be associated with untoward side effects and significantly increases complexity and risk of poor compliance. Consultation with hypertension specialist is recommended. Agents that may be considered:
   a. **Direct Vasodilator: Hydralazine** may be used starting at 10 mg TID up to 25 mg TID with meals. May be added to regimens but MUST include a diuretic and a rate controlling agent (e.g. BB or non-DHP CCB). May be combined with isosorbide 20mg TID (this combination useful in patients with intolerance to ACEI/ARB). As with minoxidil must monitor for CHF, tachycardia, and volume overload.
   b. **Central Alpha Agonist: Clonidine po** *is short acting, unpredictable, and is not recommended. BP tends to oscillate rapidly and the rebound effect can be serious if stopped abruptly. It is better used as a* ***patch*** *every 7 days (it is expensive if not covered by a drug plan).* If a centrally acting drug is needed consider **Guanfacine** 1-2mg HS, or **reserpine** at low dose (0.1 to 0.2 mg per day). It takes at least 4 weeks to see the effect of this drug but it can be very effective combined with diuretics.

7. **Beta Blocker:** Include as appropriate for compelling indications (e.g. CAD, CHF, Afib). **Atenolol** is most effective if used BID, start at 25 mg BID (max dose in patients with GFR <30, 25-50 mg/day). Other generic beta blockers are also adequate. Bisoprolol and short acting metoprolol tartrate (Lopressor) are generic drugs also. Always use metoprolol tartrate twice a day. Metoprolol succinate (Toprol XL) is used once a day. ***Monitor HR and do not titrate dose up if resting HR is <60 bpm.***

Figure 1 Continued.

baseline to the first 24 months of follow-up on 1618 patients enrolled through March 23, 2020, who had at least one follow-up visit are included in this publication. Among those 1618 included, 39% are women, 9.6% are nonwhite, the mean age is 69.7±7.8 years, and the median follow-up is 1.95 years. The number of patients

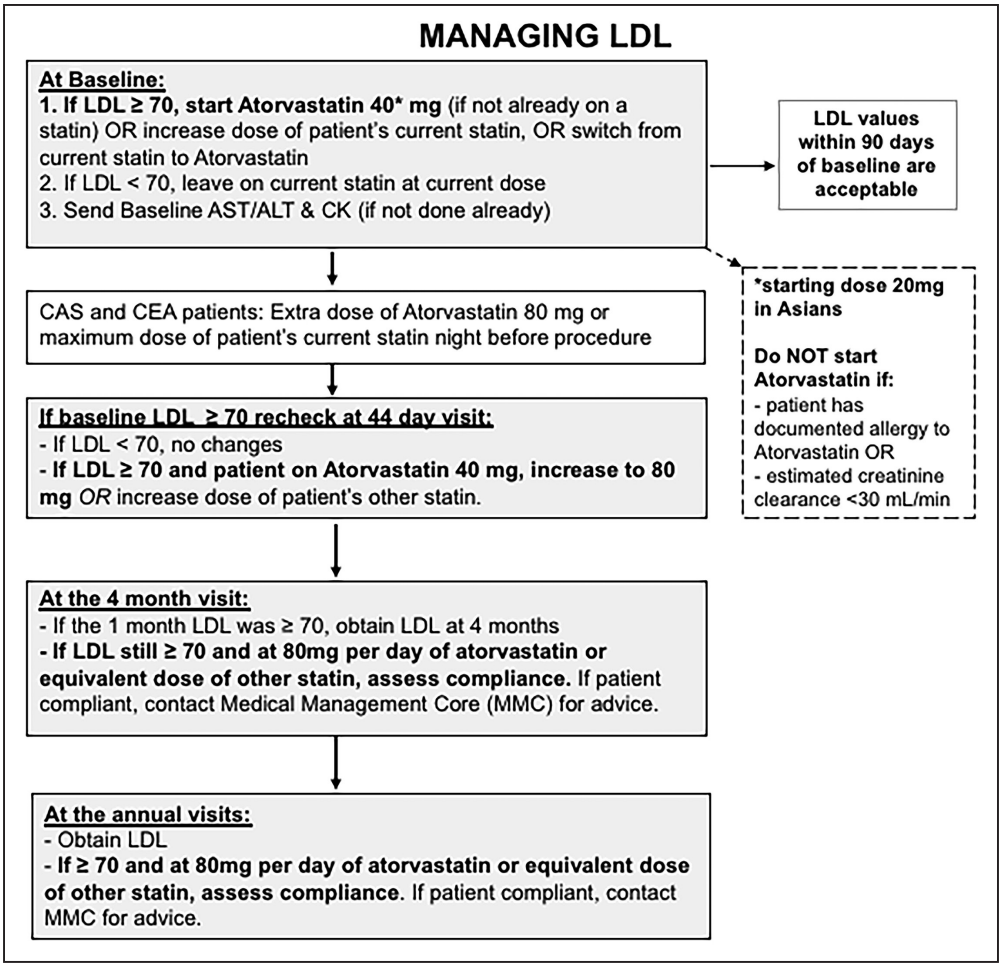

Figure 2. LDL (low-density lipoprotein) management algorithm.
AST indicates aspartate aminotransferase; ALT, alanine aminotransferase; CAS, carotid artery stenting; CEA, carotid endarterectomy; CK, creatine kinase; and MMC, CREST2 Medical Management Core.

designated as risk factor target failures was 5 for LDL and 21 for SBP. The number of visits with orthostatic hypotension (standing BP drop ≥15 mm Hg) was 366/4799 (7.6%). At baseline, the mean (±SD) LDL was 80.5±35.5 mg/dL and the mean (±SD) SBP was 139.7±20.2 mm Hg, which improved to 66.7±29.3 mg/dL and 130.3±17.6 mm Hg at the last recorded follow-up visit. The changes in LDL and SBP control over the first 2 years of follow-up are shown in Figure 3.

The percentage of patients in-target for each risk factor at baseline and the last follow-up visit up to 24 months are shown in Table 2. There was significant improvement in control when comparing last follow-up visit to baseline for all risk factors, particularly the primary risk factors hyperlipidemia and hypertension. The proportion of patients in-target improved from 45% to 67% for LDL and from 43% to 61% for SBP (both changes $P<0.001$). Because the SBP target changed to <130 mm Hg after some patients left the study (as detailed in Appendix I in the Data Supplement), we excluded 602 patients who did not have a follow-up visit after the new target was implemented and found the percent in-target improved from 46% at baseline to 70% at last follow-up. Similarly, the mean (±SD) SBP improved from 138.4±19.9 mm Hg at baseline to 128.5±16.9 mm Hg as last follow-up.

Baseline factors associated with being in-target for LDL and SBP at last follow-up in multivariate analyses are shown in Table 3 (univariate in Appendix III in the Data Supplement). Patients were more likely to be in-target for SBP at last follow-up if they were in-target at baseline, younger, smoking, and not diabetic. Patients were more likely to be in-target for LDL at last follow-up if they were in-target at baseline, male, and had no diagnosis of depression.

DISCUSSION

CREST2 is designed to evaluate whether, among patients with severe asymptomatic carotid stenosis, intensive contemporary medical therapy can obviate the need for revascularization for stroke prevention. Applicability of the final CREST2 results requires that the most modern, evidence-based medical practices are provided to patients and that successful risk factor control is achieved. Thus far, our multimodal approach to risk factor

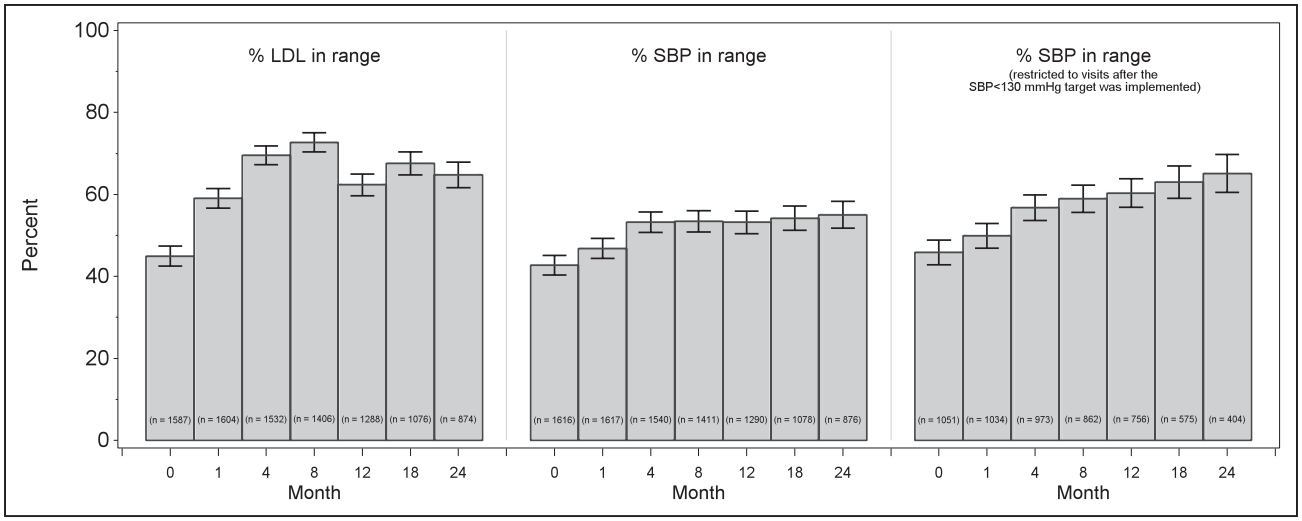

Figure 3. The percent of patients (with 95% confidence bounds) in-target for LDL (low-density lipoprotein; <70 mg/dL) and systolic blood pressure (SBP; <130 mm Hg) at follow-up visits.
SBP is shown both overall and including only patients who had a follow-up visit after the new SBP target was implemented (previously <140 mm Hg). The number of recorded values at each visit for each parameter is shown inside of the bar. A McNemar test of differences in the proportion in-target compared with baseline was significant for follow-up visits for both LDL and SBP at $P<0.0001$, except for the following: 1. SBP overall comparing baseline to 1 mo ($P=0.0021$) and 2. SBP limited to visits occurring after target changed comparing baseline to 1 mo ($P=0.0080$).

control has resulted in significant early improvements in control of the primary risk factors, hyperlipidemia, and hypertension. Improvement in LDL and SBP was seen within 1 month of enrollment and maintained throughout 2 years, suggesting that adherence to the protocol was maintained. As seen in prior studies,[31–34] our interim results suggest that risk factor control during follow-up in CREST2 may be related to patient age, sex, and the presence of risk factors such as diabetes mellitus, smoking, and depression. Patients who were in-target at baseline were also more likely to be in-target at last follow-up, as expected. The baseline predictors of risk factor control will be further explored at the end of the study.

Of note, over half of CREST2 patients were not in-target for LDL and SBP at their baseline study visit. This finding is consistent with prior reports indicating that achievement of risk factor treatment targets is suboptimal in many clinical practices,[35–39] with <40% of Americans >60 years old meeting >2 of 7 American Heart Association ideal cardiovascular metrics.[40] Inadequate risk factor control before study entry may be the result of physician and patient treatment inertia, or lack of access to the necessary resources (eg, medications or expertise). Higher LDL at baseline may reflect a trend in practice away from treating to target, although recent guidelines[28,41,42] and clinical trial data[43] support targeting LDL <70 mg/dL in patients with atherosclerosis. Similarly, changes in recommended BP targets[22] may have also impacted baseline control. Nevertheless, demonstration of improvement in risk factor control during CREST2 suggests that the patients were not medically refractory.

To provide cutting-edge medical care to CREST2 patients, the IMM protocol has been modified to incorporate practice changes, such as the added availability of a PCSK9 inhibitor and lowering the SBP target to be consistent with national guidelines. Because the

Table 2. CREST2 Risk Factor Control at Baseline and Last Follow-Up*

Risk Factor	Baseline Number (% in-Target; n=1618)	Last Follow-Up* Number (% in-Target; n=1618)	% Improvement	*P* Value†
SBP <130 mm Hg	690 (43%)	990 (61%)	18%	<0.001
LDL <70 mg/dL	713 (45%)	1060 (67%)	22%	<0.001
Smoking	1279 (79%)	1323 (82%)	3%	<0.001
Physical activity	793 (49%)	915 (57%)	8%	<0.001
BMI	378 (23%)	508 (31%)	8%	<0.001
HbA1c‡	291 (47%)	317 (51%)	4%	0.01

BMI indicates body mass index; CREST2, Carotid Revascularization and Medical Management for Asymptomatic Carotid Stenosis; HbA1c, hemoglobin A1c; LDL, low-density lipoprotein; and SBP, systolic blood pressure.
*Within 24 mo.
†Comparison of follow-up to baseline using McNemar test.
‡Data limited to the 620 patients with diabetes mellitus or on medication.

Table 3. CREST2 Baseline Factors Associated With Target Achievement at Last Follow-Up

Baseline Characteristic	OR (95% CI)	*P* Value
SBP in-target at last follow-up*		
SBP in-target at baseline	2.09 (1.7–2.6)	<0.0001
Age per 10 y	0.86 (0.75–0.99)	0.03
History of diabetes mellitus	0.76 (0.61–0.94)	0.01
Smoking†	1.40 (1.08–1.82)	0.01
LDL in-target at last follow-up*		
LDL in-target at baseline	5.4 (4.2–6.9)	<0.0001
Male sex	1.42 (1.13–1.78)	0.003
History of depression	0.72 (0.52–0.999)	0.049

CREST2 indicates Carotid Revascularization and Medical Management for Asymptomatic Carotid Stenosis; LDL, low-density lipoprotein; OR, odds ratio; PACE, Physician-Based Assessment and Counseling for Exercise; and SBP, systolic blood pressure.

*Up to 24 mo.

†In-target for smoking determined by PACE score.

most up-to-date risk factor control strategies are used, the results should be generalizable to most modern clinical practice settings. Criticisms of the SAMMPRIS multimodal IMM approach, which is similar to that used in CREST2, included the use of a lifestyle coach and central oversight of risk factor performance as not real world.[44] Lifestyle coaching is recommended by the American Heart Association guidelines[45] and has moved beyond the traditional healthcare establishment (eg, cardiac rehab) to other settings, such as the workplace and home. According to a recent survey of >1500 companies of various sizes, wellness programs are provided by over half of all employers,[46] and among large US employers, the majority offer comprehensive wellness programs that include coaching for lifestyle modification.[47] Access to health and wellness applications by smartphone/tablet owners is also on the rise, with data from 2016 indicating that 42% of US smartphone or tablet owners use ≥1 fitness application and 18% use a health or wellness coaching service.[48] Therefore, wellness and lifestyle coaching are now widely accessible and part of the real world for many individuals in a variety of settings. However, access to such programs may be limited in older patients who may not be employed or familiar with wellness applications.

Oversight of site performance for achievement of prevention measures is also a real-world evidenced-based practice now that is used extensively in clinical practice settings to improve outcomes. One integrated healthcare delivery system in Northern California nearly doubled the hypertension control rates of its healthcare providers by implementing performance feedback and standardized blood pressure algorithms[49] similar to those from CREST2. Similarly, the combination of audit and feedback programs with ongoing education and training has also been used to improve control of risk factors in high-risk populations.[50,51] A recent Cochrane review of >100 reports that studied clinical practice audit and feedback programs found important improvements in clinical practice outcomes.[52] Due to the success and potential cost savings of such feedback programs, healthcare reimbursement models have shifted toward value-based care (ie, pay-for-performance), which incentivizes healthcare systems and practitioners for achieving targets or quality measures. Initially, value-based care models were mostly limited to government-paid insurance programs, but are now utilized by almost half of the US large health insurers.[53]

In summary, advances in the management of vascular risk factors over the last 20 years have resulted in declines in stroke morbidity and mortality. Over the past decade, multimodal IMM of vascular risk factors has now been shown to obviate the need for revascularization in several vascular conditions.[11,12,14,54] The CREST2 trial is designed to determine if these medical advances have improved enough to obviate the need for revascularization in patients with asymptomatic carotid stenosis. The medical management strategy in CREST2 uses a multimodal approach to risk factor control to provide cutting-edge medical care. Thus far, this multimodal approach has been very effective in achieving risk factor targets (particularly for LDL and SBP) in prior trials and in CREST2. Intensive management of vascular risk factors should be incorporated into the management of patients at risk of stroke due to atherosclerosis both in clinical practice and in future stroke prevention trials.

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Supplemental Materials

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Appendix I: Rationale for CREST2 Risk Factor Targets
Appendix II: INTERVENT Interaction With the Patients, Sites, and Medical Management Core
Appendix III: CREST2 Baseline Factors Associated With Target Achievement of SBP and LDL at Last Follow-Up Univariate Results

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