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Coronary Heart Disease Risk Factors and Outcomes in the Twenty-First Century: Findings from the REasons for Geographic and Racial Differences in Stroke (REGARDS) Study

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Abstract

REasons for Geographic and Racial Differences in Stroke (REGARDS) is a longitudinal study supported by the National Institutes of Health to determine the disparities in stroke-related mortality across USA. REGARDS has published a body of work designed to understand the disparities in prevalence, awareness, treatment, and control of coronary heart disease (CHD) and its risk factors in a biracial national cohort. REGARDS has focused on racial and geographical disparities in the quality and access to health care, the influence of lack of medical insurance, and has attempted to contrast current guidelines in lipid lowering for secondary prevention in a nationwide cohort. It has described CHD risk from nontraditional risk factors such as chronic kidney disease, atrial fibrillation, and inflammation (i.e., high-sensitivity C-reactive protein) and has also assessed the role of depression, psychosocial, environmental, and lifestyle factors in CHD risk with emphasis on risk factor modification and ideal lifestyle factors. REGARDS has examined the utility of various methodologies, e.g., the process of medical record adjudication, proxy-based cause of death, and use of claim-based algorithms to determine CHD risk. Some valuable insight into less well-studied concepts such as the reliability of current troponin assays to identify “microsize infarcts,” caregiving stress, and CHD, heart failure, and cognitive decline have

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Compliance with Ethics Guidelines

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also emerged. In this review, we discuss some of the most important findings from REGARDS in the context of the existing literature in an effort to identify gaps and directions for further research.

Keywords

REGARDS; Coronary heart disease; Coronary risk factors

In 1965, a clustering pattern of excess mortality from stroke was noticed in the South Central and South Atlantic states of the USA [1]. This clustering region has been identified as the “stroke belt” and includes the states of North Carolina, South Carolina, Georgia, Alabama, Mississippi, Arkansas, Louisiana, and Tennessee [1, 2] Within the “stroke belt,” a region of even higher mortality has been identified as the “stroke buckle,” which includes coastal areas of North Carolina, South Carolina, and Georgia [3–5]. Like excess stroke mortality in the Southeast USA, the cause underlying the excess stroke mortality among African-Americans (AAs) remains enigmatic. The REasons for Geographic and Racial Differences in Stroke (REGARDS) study is a longitudinal cohort study of 30,239 US AA and white adults ≥45 years of age. In addition to providing national data on stroke incidence and prevalence of stroke risk factors and assess geographic and racial differences in prevalence of these risk factors, the objective of the REGARDS study is to determine the causes of excess stroke mortality in the “stroke belt,” especially among AAs. REGARDS participants were enrolled from January 2003 to October 2007. The participants (42 % AAs and 55% female) were randomly sampled with recruitment by mail followed by telephone contact, after which data on sociodemographic, comorbidities, lifestyle, and psychosocial factors were collected. Subsequently, home visits were scheduled to conduct physical measurements and collect blood and urine specimens. The participants were followed via telephone every 6 months for detection of potential study endpoints, and medical records were adjudicated by an expert panel. The REGARDS–Myocardial Infarction (MI) ancillary study has resulted in a body of work that has contributed to our understanding of the underlying mechanisms leading to disparities in CHD outcomes. The goal of this manuscript will be to review the findings of the REGARDS study as it relates to CHD, compare REGARDS study findings to the published literature, and identify gaps in the evidence to guide future research.

This review has been divided into six sections (Table 1) to address the various aspects of CHD-related findings reported in REGARDS through 2014. Each of the topics in Table 1 is discussed separately with summary tables provided for REGA RDS findings.

Incidence

Among the 1821 US counties represented in REGARDS, those in the highest tertile of CHD mortality formed a crescent-like band stretching from the Northeast towards Texas and extending into New Mexico, Southern California, and Southwestern Nevada (Table 2) [6]. REGARDS has revealed important racial and gender disparities in prevalence of CHD in the study population. In REGARDS, AAs were at twice the risk for incident fatal myocardial infarction (MI) than whites [7••]. In AA compared to whites, this increased risk was associated with increased prevalence of CHD risk factors, such as smoking, diabetes,

obesity, systolic blood pressure (SBP), and impaired renal function [7••]. The decline in rates of acute MI and CHD is steeper in whites than in AAs, and this widening disparity has been reported in several studies [8–10]. Among men, AAs compared to whites had a lower risk of incident nonfatal MI that persisted after adjusting for CHD risk factors [7••]. In contrast, among women, AAs compared to whites had a higher risk of incident nonfatal MI, and the difference was attenuated after adjusting for CHD risk factors. These findings highlight the racial differences in CHD risk factors and illustrate that racial and gender disparities are frequent and vary dependent upon the outcome. The following sections will attempt to identify factors contributing to these racial differences in the CHD risk profile.

Risk Factors

Blood Pressure

Pre-Hypertension—Prehypertension is defined by the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC 7) as a SBP of 120–139 mmHg and/or a diastolic blood pressure (DBP) of 80–89 mmHg (Table 3) [11]. However, the 2014 evidence-based guideline for the management of high blood pressure in adults report from the Panel Members Appointed to the Eighth Joint National Committee (JNC 8) did not comment on treatment of prehypertension, as that guideline uses BP thresholds to guide pharmacologic treatment [12]. The presence of prehypertension has been associated in some but not all studies with an increased risk of MI, congestive heart failure (CHF), stroke, and CHD [13, 14]. Importantly, there is a lack of data describing racial differences in the prevalence of prehypertension and its association with cardiovascular (CV) risk factors.

In REGARDS, the prevalence of prehypertension was reported to be 17 %; however, the prevalence was 51 % when excluding patients with hypertension [15]. The prevalence of prehypertension was higher in AAs compared with whites across all age groups and geographic regions. Prehypertension was more prevalent in obese individuals and those with self-reported heart disease. Prehypertension was associated with elevated high-sensitivity C-reactive protein (hsCRP) levels, diabetes mellitus (DM), microalbuminuria, and heavy alcohol consumption [15, 16].

In REGARDS, a report of 24,388 patients (followed for a mean of 4.2±1.5 years) found that prehypertension was not associated with incident acute CHD (nonfatal MI and death) [17]. This is consistent with the findings of a study involving 9087 subjects from the National Heart and Nutrition Examination Survey (NHANES) cohort that reported no association of prehypertension with cardiovascular mortality [18]. In contrast, among 6859 subjects of the Framingham Heart Study (FHS) cohort, prehypertension (defined as a SBP of 130–139 and DBP 85–89) was associated with an increased risk of major CV events [19]. Since REGARDS consists of a population-based sample with national distribution, and includes (compared to many other studies) a higher percentage of AAs and women, these previous studies in a more restricted population may possibly explain some of the disparate results. REGARDS findings may help to increase understanding of the inconsistencies surrounding the association of prehypertension and CV risk.

Medication Nonadherence—Nonadherence to medications has been linked to poorly controlled BP, increased CHD events, and increased physician visits and hospitalization, and, ultimately, increased healthcare costs [20–22]. Among REGARDS participants ≥55 years of age taking antihypertensive medications, SBP between 120 and 139 mmHg was associated with decreased risk for CV and all-cause mortality compared to SBP ≥140 mmHg [23]. A linear association was observed between SBP ≥140 mmHg and all-cause mortality among all participants except those ≥75 years old. In light of current debate regarding appropriate BP levels in the elderly, the above findings reinforce the importance of adherence to antihypertensive medications to reduce CHD risk [23–25].

In REGARDS, low medication adherence was associated with increased SBP and the percentage of subjects with uncontrolled BP [26]. Medication nonadherence was more common among AAs than whites in REGARDS, and AAs were more likely to have BP >140/90 mmHg regardless of the degree of medication adherence. Despite the concept that cost is an important driver of medication nonadherence, the percentage of antihypertensive medications available in generic form was not linked with better control of BP [27•], although the availability of generic medications has been shown in other studies to improve BP control in AAs (overall control of SBP in diabetics improved from 2003 to 2007 in both AAs and whites) [28, 29]. In REGARDS, among AA diabetic men with annual income less than $35,000, medication nonadherence was independently linked with lack of diabetes-specific BP control (i.e., <130/80 mmHg) [27•]. The odds of AAs having BP <130/80 mmHg were 39%lower than whites and were 66 % lower in men than in women [29]. In light of the prevailing racial and gender disparities in BP control, these findings highlight the continued need for more effective interventions to achieve both medication adherence and BP control, especially in AAs.

Psychosocial, Behavioral, and Environmental Factors—The lack of BP control in AAs remains enigmatic because in REGARDS, AAs compared to whites have been shown to be more intensely treated, and this difference persisted across all ages, sex, income, education categories, and geography [30]. One potential explanation for this disparity in BP control between AAs and whites could be due to psychosocial factors such as lack of trust in physicians or access to health care (associations that are generally not well studied) [31, 32]. BP control rates have been shown to be higher in AAs and whites when they are treated at the same health-care facility and by the same provider [31]. However, in REGARDS, trust in physicians was not related to BP control [33]. In particular, although lower trust in physicians was found among AAs compared to whites, this lack of trust was not associated with racial disparities in BP control.

Access to care may be another important influence on disparities in BP control. Health Professional Shortage Areas (HPSA) are federally designated geographic regions based on population size and physician availability [34]. The HPSA designation involves a complex process that factors in the ratio of provider to patients, underserved populations or sociodemographic uniqueness, and health-care facilities that provide primary care services to a population group [6, 34]. REGARDS has shown that, while awareness of chronic conditions such as hypertension was greater among uninsured participants in HPSA compared with uninsured participants in non-HPSA, the rates of treatment were similar in

both groups, but the odds of BP control were lower in the former compared with the latter [35]. Consistent with this evidence, a study of 6023 hypertensive participants in REGARDS showed that the odds of hypertension awareness was 40 % higher and of receiving treatment 60% higher among AAs compared to whites [36]. However, among those receiving antihypertension treatment, AAs had 30 % lower odds of achieving controlled BP. There were no substantial differences in hypertension awareness between stroke belt and nonstroke belt areas, but there was a trend towards better treatment and control of hypertension in the stroke belt areas [36]. Federally designated HPSA residents may have increased awareness of chronic diseases, but adequate management of these chronic conditions remains an issue. Results from REGARDS highlight the need for better strategies to ensure health awareness among uninsured HPSA residents with chronic conditions like hypertension.

In addition to psychosocial factors, environmental factors such as outdoor temperature and seasonal variations have been known to influence BP [37, 38]. In REGARDS, the association of outdoor temperatures and BP levels were assessed using the National Aeronautics and Space Administration's (NASA) daily maximum and minimum temperatures on the same day as the in-home visit as well as the average of 2 weeks prior to the in-home visit [39]. The results suggested that the time of year was of secondary importance to the association of BP and temperature. Colder temperatures were associated with higher BPs, although the magnitude of the change was small (on the order of a few mmHg). The association of temperature and BP was independent of age, race, sex, and geographical region. These findings suggest that temperature has a small influence on BP, but might be considered when disparities in hypertension are assessed.

Obesity (and its anthropometric distribution, i.e., the body's fat distribution) is a known cardiovascular risk factor with the prevalence of obesity increasing rapidly in the USA [40]. Obesity-related hypertension is driven by activation of the rennin–angiotensin–aldosterone system, sympathetic nervous system, and salt retention [41]. REGARDS reported that moderately increased waist circumference (80–88 cm in women, 94–102 cm in men) was associated with hypertension-independent of body mass index (BMI) [42]. Within each category of BMI (normal, overweight, and obese), the odds of being hypertensive increased with increasing waist circumference. These findings were independent of the geographical region and were similar for whites and AAs.

As aforementioned, medication adherence has been associated with BP control [43]. Factors such as negative attitudes towards medications, lack of understanding of the functional effect of medications, lack of understanding of the future risks incurred by disease, and a host of psychosocial factors may lead to medication nonadherence [44, 45]. In REGARDS, participants with chronic kidney disease (CKD), defined as epidermal growth factor receptor (eGFR) <60 ml/min/1.73 m^2, 30 % forgot to take or were careless about taking their medications when they felt either better or worse. That REGARDS analysis also found no difference in antihypertensive medication adherence rates among participants with or without CKD [46], possibly reflecting low awareness of either the presence of CKD and/or the importance of BP control in participants with CKD.

Apparent Treatment Resistant Hypertension—Some individuals may not achieve BP control despite intensive treatment. Apparent treatment-resistant hypertension (aTRH) is a term used to describe individuals who, regardless of their BP control, require treatment with at least three classes of antihypertensive medications at optimal doses (with one of them being a diuretic) [47]. aTRH is further divided into controlled aTRH (≥4 medication classes but with controlled BP) and uncontrolled (≥3 medication classes with uncontrolled BP) [48]. Failure to control BP in the setting of medication nonadherence has been called pseudoresistance [47]. An important finding from REGARDS was the higher prevalence of medication nonadherence (i.e., pseudoresistance) among those diagnosed initially with aTRH (8.1 % with nonadherence vs 5 % without). Female gender, residence outside of the stroke buckle or belt, lack of physical activity, and presence of depressive symptoms were also associated with pseudoresistance [49].

Regardless of adherence, aTRH has been associated with an increased prevalence of cardiovascular risk factors and a higher 10-year Framingham Risk Score (FRS). However, there are insufficient data from prospective studies in individuals with aTRH for CHD risk to be reliably estimated [50–52]. In REGARDS, aTRH was associated with an increased risk of acute CHD and all-cause mortality, and participants with uncontrolled compared to controlled aTRH were at increased risk for CHD [48]. In addition, aTRH was associated with a higher risk of incident end-stage renal disease (ESRD), and was greater in those with uncontrolled compared with those with controlled aTRH [53]. Similar findings were shown in the Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), in which aTRH was associated with CHD, all-cause mortality, stroke, and ESRD. [54] These findings collectively support the need for continued efforts to identify the underlying mechanisms of aTRH and to develop more effective treatment options.

Aside from medication adherence, the question remains as to whether patients with aTRH are treated optimally. In REGA RDS, among participants receiving antihypertensive treatment, 0.5 % (*n*=78) were taking ≥5 classes of antihypertensive medications (i.e., refractory hypertension) [55]. Inconsistent with evidence-based guidelines [47], only 18 % of these participants were receiving mineralocorticoid receptor antagonists (MRAs) as a part of their antihypertensive regimen. In addition, participants with refractory hypertension were noted to have a higher 10-year FRS compared to those with resistant or controlled hypertension. Further research is needed in these extreme cases to better understand the pathophysiological mechanisms and develop treatment modalities to control BP. The role of unhealthy life style factors in patients with aTRH has been suggested [47, 56]. Guidelines recommend smoking cessation, moderation of alcohol consumption, regular exercise, weight loss, and dietary modifications concordant with the Dietary Approaches to Stop Hypertension (DASH) diet, which emphasizes low sodium intake and consumption of a low fat and high fiber diet [11, 57]. In REGARDS, a greater number of healthy life style factors (such as normal waist circumference, physical activity, nonsmoking, moderate alcohol consumption, low sodium/potassium intake ratio, and DASH diet) was associated with lower risk for CHD events. Among the healthy life style factors, physical activity and nonsmoking were associated with lower risk of CHD mortality [58]; however, the association of unhealthy lifestyle factors as it applies to aTRH is less well studied. In REGARDS, in those

taking ≥3 antihypertensive medications, there was higher prevalence of unhealthy lifestyle risk factors such as obesity, physical inactivity, smoking, heavy alcohol use, low adherence to a DASH diet, and high salt intake [59]. However, there was no association between the aforementioned risk factors and aTRH [59]. These findings highlight the need to determine whether life style modification plays a significant role in mitigating the risks of aTRH.

Pulse Pressure—Pulse pressure (PP), the difference between SBP and DBP, is an indicator of arterial stiffness and has been reported to be a predictor of fatal MI, fatal stroke, and cardiovascular events [60–62]. PP has also been linked with increased CHD risk in whites, but less is known about the relationship between PP and CHD in AAs [63, 64]. In REGARDS, a linear increase in the risk of CHD (including combined fatal and nonfatal MI) was associated with increasing PP, independent of SBP and regardless of age, gender, region, or race, suggesting that PP is similarly deleterious for AAs and whites [65].

Prediabetes and Diabetes

Prediabetes (fasting blood sugar, 100–125 mg/dL, or hemoglobin A_1C, 5.7–6.4 %) has been associated with an increased risk of microvascular complications and CV disease (Table 4) [66, 67]. Although the association of prediabetes and atherosclerosis remains uncertain, it is essential to optimize the CV risk profile among those with prediabetes [68]. In REGARDS, there was increased prevalence of prediabetes in AAs compared to whites regardless of the region of residence, and there was increased prevalence of prediabetes in both whites and AA living in the stroke belt [69]. Since the progression of prediabetes to type 2 DM (fasting blood sugar, ≥126 mg/dL, or hemoglobin A_1C, ≥6.5 %) can be delayed [67], these findings could help to direct preventive strategies aimed at certain populations and geographic regions with higher prevalence of prediabetes.

Diabetes is a major cardiovascular risk factor [70]. In REGARDS, control of DM was 21 % lower in counties with the highest vs the lowest CHD mortality tertiles despite similar levels of awareness and treatment [6]. In addition, there was no significant association between the counties' HPSA status and awareness, treatment, or control of DM and CHD mortality tertile. Importantly, there was no association between counties with high CHD mortality and HPSA status, suggesting that current approaches to assigning HPSA status are not necessarily resulting in extra resources reaching the highest need areas [6]. A study contrasting findings in individuals with and without diabetes from the combined Atherosclerosis Risk in Communities (ARIC) and REGARDS databases reported a decrease in the incidence of CHD and CHD mortality between 1987 and 1996 (ARIC) and 2003 and 2009 (REGARDS) [71]. This decrease was attributed to a decline in mean low density lipoprotein cholesterol (LDL-C) as a result of the use of lipid lowering medications. However, in both time periods, the incidence of CHD and CHD mortality remained two to three times higher in participants with vs without DM. These findings support the need for continuing efforts at diabetes prevention and CV risk factor management.

Dyslipidemia

In REGARDS, there was no difference in awareness of treatment of dyslipidemia in high- and low-CHD-mortality counties (Table 5). However, compared to counties with lowest

CHD mortality, those with high mortality had 17 % lower odds of dyslipidemia control [6]. Furthermore, there was no significant association between the HPSA status of the counties and awareness, treatment, or control of dyslipidemia [6]. In REGARDS, the overall prevalence of dyslipidemia was 55 %; although AAs had lower prevalence, compared with whites, AAs were less likely to be aware, treated, or controlled [72]. The failure of lipid control in AAs may put them at a higher CHD risk. The reasons for this disparity in dyslipidemia awareness, treatment, and control warrants further investigation.

Diet and Obesity

Among the many reasons proposed for the higher CVD mortality in the stroke belt are regional and racial differences in dietary practices (Table 6) [73, 74]. For example, among men, AAs compared to whites had lower intake of all nutrients (i.e., potassium, sodium, calcium, and magnesium) except fiber. Compared to white men, AA men had a higher cholesterol intake, but had 1 % less intake of saturated fat [75]. Compared to other geographic regions, the areas in stroke belt and buckle had higher intake of cholesterol and lower intake of fiber, saturated fat, calcium, potassium, sodium (in stroke belt only), and magnesium (in stroke buckle only) [75]. Therefore, a comparison of dietary intakes and preferences may help understand the racial and geographic health disparities and could also help shape population-specific dietary recommendations.

In 2011–2012, about 35%of US adults >20 years old were obese (BMI≥30 kg/m^2) [40]. However, obesity, as defined by BMI, fails to take total body fat distribution into account [76]. Waist circumference or waist/hip ratio (which correlates with abdominal adiposity) is more strongly associated with cardiovascular morbidity and mortality [77]. In REGARDS, among those with CKD, the survival was lowest with a BMI of 18.5– 24.9 kg/m^2 and ≥40 kg/m^2 [78]. An increase in waist circumference was associated with a linear increase in all-cause mortality, with the highest mortality when waist circumference was ≥98 cm in women and ≥112 cm in men (with reference being <80 cm in women and <94 in men). Within each BMI category, the mortality rates were generally higher with waist circumference ≥98 cm in women and ≥112 cm in men. REGA RDS also found racial disparities in mortality associated with BMI and waist circumference [79]. Whites with BMI <20 and ≥35 kg/m^2 had a higher risk for mortality than those with BMI 20–24.9 kg/m^2; however, unlike whites, AAs with BMI ≥35 kg/m^2 did not have a higher risk for mortality. In whites, the waist circumference cutoff >90 cm in women and >100 cm in men was associated with higher risk of mortality. The similar cutoff of waist circumference in AA women and men resulted in 29 and 3 % greater risk of mortality, respectively. Given that waist circumference (>88 cm in women and 102 cm in men) is part of the metabolic syndrome [80], these findings suggest that BMI (a function of total body fat and muscle mass) should be used in conjunction with waist circumference (a measure of abdominal fat) to determine the true risk of CHD mortality.

In 2006, the International Diabetes Federation (IDF) modified the Adult Treatment Panel (ATP) III classification of metabolic syndrome by lowering the cutoff points for defining elevated waist circumference (from ≥40 in to ≥37 in in men and ≥35 in to ≥31.5 in in women) [81, 82]. In REGARDS, using waist circumference and central obesity, individuals

meeting ATP III compared to IDF criteria for metabolic syndrome had a greater prevalence of CV disease and had a higher proportion of individuals with elevated CHD risk [83]. However, individuals with IDF criteria had a twofold increased odds of having elevated CHD risk compared to those without metabolic syndrome [83]. These findings suggest that, although the ATP III criteria help to identify a high-risk group, the use of the IDF criteria does identify additional individuals at risk who could potentially benefit from risk factor modification. In REGARDS, obesity was associated with mortality in middle- and older-aged whites but not AAs [78]. In addition, among those older than 60 years, obesity was weakly associated with mortality especially in AA, and increased waist circumference was associated with mortality among AA women but not AA men [78]. The above findings highlight the need for further research to determine the utility of measuring ectopic fat deposition and inflammatory markers (of adiposity) to detect individuals with greater CV risk.

Nontraditional Risk Factors

Chronic Kidney Disease—Chronic kidney disease (CKD) has been associated with increased risk for development of CV disease, recurrent CHD events and all-cause mortality comparable to patients with diabetes, metabolic syndrome, or smoking (Table 7) [84, 85]. CKD defined as eGFR <60 ml/min/1.73 m^2 and urinary albumin/creatinine ratio (ACR)>10 mg/g has been independently associated with all-cause mortality in the general population [86]. A REGARDS study advanced the understanding of this relationship by reporting that higher urinary ACR (comparing ≤10 mg/g, 10.1–29.9 mg/g, 30–300 mg/g, and >300 mg/g) but not urinary albumin excretion was independently associated with incident CHD (nonfatal MI and CHD death); the magnitude of this association was greater in AAs than in whites [87]. This study reinforces the utility of ACR as a biomarker for CHD risk and underscores the need for a better understanding of the excess risks conferred by ACR among AAs [88, 89].

The American Heart Association (AHA) has developed a metric called Life's Simple 7 to reflect general CV health [90]. Life's Simple 7 proposes that body weight, cigarette smoking, diet, physical activity, BP, cholesterol, and glucose levels are components of CV health. There are few data on the association of Life's Simple 7 risk factors and end-stage renal disease (ESRD) [91]. A REGARDS study showed that, compared to those with 0 or 1 ideal factors in Life's Simple 7, those with ≥2 ideal factors had lower risk of all-cause mortality and progression to ESRD [91], suggesting that optimizing modifiable CV risk factors could prevent worsening of renal function and that their impact in preventing CKD could be increased if patients were aware of their CKD status [92, 93]. REGARDS participants with or without CHD had low awareness of their CKD (5%in those with CHD vs 2%in those without CHD) [94]. In addition, the study found that CKD awareness was associated with tobacco avoidance, but not with physical activity, optimal BP, glycemic control, avoidance of nonsteroidal anti-inflammatory drugs, or use of angiotensin-converting enzyme inhibitors/angiotensin receptor II blockers (ACEI/ARB) [95]. Individuals with reduced eGFR are less likely to be treated in hospital or discharged with optimal medications after a CHD event [96, 97].These studies were conducted in inpatient setting, and there is lack of data in the outpatient setting. In REGARDS, among participants with

CHD, those with eGFR <45 and 45–59 ml/min/1.73 m^2 compared to those with eGFR≥60 ml/min/1.73 m^2 had similar or even higher rates of medication use such as beta-blockers, ACEI or ARBs, statins, or antiplatelet agents [98]. However, the study also found that the overall use of these medications was suboptimal (59.8 % used antiplatelet agents, 49.9 % used ACEI/ARB, 41.6 % used beta-blockers, and 53 % used statins), and the rate of nonadherence was 30 % [98]. These findings suggest that providers may defer use of certain medications in individuals with CKD during or soon after an acute event to prevent any adverse effects [98]. This highlights the need for a better understanding of barriers to awareness, risk factor modification, and adequate treatment among individuals with CKD and that this approach may lead to better CHD outcomes.

Atrial Fibrillation with or without Chronic Kidney Disease—Atrial fibrillation (AF) is more prevalent in individuals with advanced CKD, particularly in those on hemodialysis [99]. However, the burden of AF among those with less severe CKD has not been thoroughly investigated. A REGARDS study reported a higher prevalence of AF in CKD participants regardless of severity (independent of race, age, and gender), but the prevalence was highest in those with stage 4–5 CKD [100]. AF has been linked with the metabolic syndrome, but these studies were conducted in select populations or were based on inpatients [101, 102]. In REGARDS, AF was linked with the presence of metabolic syndrome, and the prevalence of AF was associated with a greater number of metabolic syndrome components (hypertension, dyslipidemia, elevated blood sugar, and abnormal waist circumference) [103]. No racial differences were noted in these associations.

Underuse of warfarin in individuals with AF has been reported [104, 105]; however, it is not well known if the underuse is due to the lack of awareness of AF. However, REGARDS found that AAs were less aware of having AF and were undertreated compared to whites, independent of access to health care and health insurance [106]. In addition, women compared to men, who were aware of having AF, were one third as likely to be treated with aspirin or warfarin, putting them at a potentially higher risk of incident stroke and stroke-related mortality. Despite an increased burden of stroke among AAs, the overall prevalence of AF in AAs is lower compared to whites [107, 108]. One explanation could be related to the method used to detect AF. In REGARDS, the diagnosis of AF was based on electrocardiogram (ECG) or self-report, potentially missing cases of paroxysmal AF. Some evidence suggests that the greater the sensitivity of the method used to detect AF, the greater the attenuation of racial and ethnic differences [109]. In REGARDS, AF was independently associated with incident MI with a stronger association in AAs and women compared to whites and men [110]. In addition, warfarin use in AF was associated with a decreased risk of MI. Interestingly, the prevalence of AF in REGARDS was not higher in the stroke belt [111]. These findings highlight the importance of improved AF detection and use of anticoagulation.

Depression and Psychosocial Factors—Post-MI depression has been linked with a twofold increase in all-cause and CHD mortality [112]. In REGARDS, a strong and graded correlation was shown between depressive symptoms (as assessed by Centers for Epidemiologic Studies of Depression (CESD-4) scale) [113] and adverse CV health as

reflected by Life's Simple 7; the strongest association between depression and cardiovascular health was observed for smoking and physical inactivity [114]. In CHD patients in REGARDS, the association of depressive symptoms with MI or death was partially explained by smoking and physical inactivity, and the association of depressive symptoms with death was stronger than with MI. Medication nonadherence and alcohol consumption did not attenuate the association, suggesting that the presence of depressive symptoms increases the risk of death by mechanisms other than recurrent MI [115].

Psychosocial stressors have been associated with depressive symptoms [116, 117]. In particular, caregiving creates emotional stress and is associated with poor physical and psychological health, and increased mortality [118, 119]. However, the role of stress on physical health of caregivers and its differential impact by race and sex have not been well studied. In a cross-sectional study of REGARDS, highly stressed caregivers were noted to be younger, male, and AA. Higher Framingham CHD risk scores were associated with older age, male sex, and depressive symptoms, whereas having a college education was associated with lower CHD risk scores compared to participants with less than a high school education. Caregiving stress was not associated with increased CHD risk scores [120].

In contrast, in REGARDS participants studied longitudinally, high perceived stress was associated with incident CHD and all-cause mortality among low, but not high-income groups independent of CV risk factors, race, and gender [121]. These findings imply that, in those with low income, stress may play an important role in contributing to the observed higher CV risk and mortality. Numerous psychosocial factors have also been associated with low medication adherence [122]. In patients with known CHD, low medication adherence has been associated with a twofold increase in adverse events [123]. It has been postulated that one of the reasons for lower medication adherence in general could be the lack of resources, (e.g., lack of insurance or access to health care).

In studies that have reported on geographic variations in the treatment of myocardial infarction and post-MI outcomes [124, 125], none have examined how residence in a HPSA affects CV-disease-related care. In REGARDS, the lack of access to primary care as defined by the HPSA classification was not associated with a decreased use of preventive medications (e.g., statins), but lack of insurance was associated with decreased likelihood of getting treated with warfarin or a statin with a stronger association in HPSA counties [126••]. These findings suggest that residence in HPSA counties is not a barrier in getting CV disease care as long as health insurance is available.

High-Sensitivity C-reactive Protein—hsCRP, a marker of inflammation, has been linked with both obesity and the future development of major CV events [127–130]. There is lack of data on association between hsCRP and CHD mortality in the setting of obesity among different ethnic groups. In REGARDS, overweight (BMI, 25–29.9 kg/m^2), obese (BMI, 30–34.9 kg/m^2), and severely obese (BMI ≥35 kg/m^2) women were more likely to have hsCRP ≥3 compared with men [79]. Among individuals with hsCRP ≥3 vs <1 mg/L, underweight (BMI, <20 kg/m^2), and normal weight (BMI, 20–24.9 kg/m^2), whites were at significantly higher mortality risk but not severely obese whites. Similar results were seen in AAs, except that severely obese AAs were at a higher mortality risk. In addition, hsCRP ≥3

mg/L was associated with mortality in underweight (BMI, <20 kg/m^2) and normal weight (BMI, 20–24.9 kg/m^2) individuals but not in severely obese (BMI, ≥35 kg/m^2) individuals, suggesting that BMI may not reflect metabolically active fat and also supporting the need to investigate the role of other inflammatory markers. These findings are consistent with other studies and collectively reflect that BMI or waist circumference may not be optimal markers of inflammation, particularly in certain populations [131, 132]. However, these findings do not mitigate the utility of hsCRP as a predictor of CV mortality.

Heart Failure and Cognition

Heart failure (HF) has been related to stroke/transient ischemic attack (TIA) by leading to cardio-embolic events and by decreasing cerebral perfusion (Table 8) [133, 134]. In REGA RDS, the odds of self-reported cerebrovascular events were greater at all BP ranges among participants with HF, but the association between HF and cerebrovascular eventswas strongest in participants with SBP <119.5 independent of other risk factors, suggesting that low BP might play causal role in that association [135]. Cerebral hypoperfusion resulting from HF has been associated with cognitive decline in patients without stroke [136]. In REGARDS, participants with probable HF (defined as presence of self-reported orthopnea and paroxysmal nocturnal dyspnea) were more likely to have cognitive impairment compared with those without HF; however, this association diminished after inclusion of patients with prior stroke. In patients with stroke/TIA, the association of HF and cognitive impairment became insignificant in the presence of depression [137•]. In addition, among participants without stroke/TIA, socioeconomic status factors significantly attenuated the association of cognitive decline and HF. Further studies are needed to determine the relationships between depression and cognitive impairment in individuals with HF.

Methodologic Considerations

Unrecognized Myocardial Infarction

Unrecognized MIs (UMIs) diagnosed by pathological Q waves on an ECG in asymptomatic individuals have a reported prevalence of 25–40 % in the elderly (Table 9) [138]. UMI has been associated with a poor prognosis and increased long-term mortality [139–141]. In REGARDS, participants with stage 3 or 4 CKD and ACR ≥30 mg/g had a 13.4%prevalence of UMI [142]. Compared to participants with no MI, participants with UMI and stage 3 or 4 CKD and those with UMI and ACR ≥30 mg/g had an all-cause mortality hazard ratio of 1.69 and 1.45, respectively, and traditional cardiovascular risk factors (e.g., age, male gender, smoking, and hypertension) were associated with UMI [142]. These findings suggest that aggressive risk factor modification in patients who have UMI should be similar to those with recognized MIs; however, although UMI are thought to have similar biological mechanisms to recognized MI, the role of primary and secondary prevention remains unclear [143, 144]. Treatment guidelines emphasize the use of aspirin, statins, beta-blockers, and ace inhibitors in recognized MI [145]. But in REGARDS, although participants with UMI compared to no history of MI were more likely to use cardioprotective medications, they were less likely to be taking cardioprotective medications compared to those with recognized MI [142]. In addition, among those with UMI, older and diabetic patients were more likely to be on cardioprotective medications, while AAs and women were less likely to be on aspirin [146].

While the gender and racial disparity in the use of these medications among those with UMI warrants further research, these findings collectively may partly explain the increased risk for CV mortality among patients with UMI.

While ECG screening might identify patients with UMI, false positives may result in treatment that leads to side effects and increased cost. Thus, ECG screening of low-risk populations has not generally been recommended [147]. However, ECG screening may be useful in a population in whom the prevalence of UMI is high. REGARDS investigators constructed assessment tools to identify a subpopulation at high risk of UMI and in whom ECG screening may be warranted [148]. The standard tool comparator consisted of demographic factors, medications, and comorbidities, while the expanded tool included the addition of psychosocial factors and physiological measures. The c-statistic for the tools was 0.638 and 0.654, respectively, below the accepted cutoff of 0.7 to be a good discriminant [148, 149]. It thus remains a challenge to identify a population with a high prevalence of UMI. Until more reliable assays and diagnostic methods are developed, the diagnosis and management of UMI will continue to pose a challenge for health-care providers.

Troponin Assays

The use of troponin assays in the diagnosis of MI has become universal. Troponin assays are becoming increasingly sensitive, and it is now possible to detect very small amounts of myocardial necrosis using these measures. Very small non-ST elevationMI (NSTEMI) may confer similar long-term risks as larger MIs, so their detection and epidemiology are important [150, 151]. In REGARDS, very small NSTEMI (defined as MI with peak cardiac troponin level <0.5 μg/L) comprised 31.3 % of nonfatal CHD events [7••]. Incidence rates for very small NSTEMIs were similar for AA and white men, but were higher in AA women compared to white women. However, many contemporary troponin assays are imprecise at very low levels [152•], leading to recommendations to use either >99th percentile of a normal healthy population or the level at which the assay achieves a coefficient of variation of 10 % as the decision threshold for abnormal troponin when treating patients with possible MI (the universal definition of MI recommends at least one value of troponin >99th percentile of healthy individuals) [152•, 153, 154]. In REGARDS, of 649 acute care US hospitals, only 2 % included the 99th percentile or the 10%coefficient of variation in their clinical reports, and themajority of hospitals reported an indeterminate range, even though that practice is no longer recommended [152•]. Thus, there is a need for consistency in troponin reporting. In REGA RDS, microsize MI (defined as peak troponin values less than five times the lowest listed upper limit of normal) and nonmicrosize MI had a similar 28-day and 1-year mortality. Subjects with heart disease compared to those without heart disease had 63 % higher odds of having a microsize MI. In addition, AAs compared to whites had 62 % higher odds of having a microsize MI. Thus, incorrect reporting of troponins may act as a barrier to obtaining timely secondary prevention in these individuals.

Electrocardiographic Parameters

Although racial differences in ECGs among AAs and whites have been described [155, 156], there are few data in a population-based sample on the prevalence of ECG abnormalities in subpopulations such as AAs or women. REGARDS reported that the

prevalence of at least one ECG abnormality [e.g., conduction, arrhythmias, QRS complex, ST–T segments, P and T waves, left ventricular hypertrophy (LVH)] was >35 % in those ≥65 years of age, with no differences between AAs and whites [157]. Among men <65 years, AAs had more abnormalities (e.g., atrial fibrillation, Q waves, and LVH) than whites. Overall, men had more ECG abnormalities than women. The corrected QT interval was longer in women than men with no racial differences. The average heart rate was greater in women than men and in AAs than whites. The prevalence of ECG abnormalities was associated with hypertension, age, and diabetes; AA men and women between ages 45 and 64 years had a higher prevalence than whites. This REGARDS study provides a comprehensive analysis of ECG abnormalities in a large biracial cohort of participants in the USA across ages above and below 65 for both men and women.

ECG-derived LVH has been associated with CHD and long-term mortality among both men and women [158, 159]. However, in the era of increasing sensitivity of troponin assays and increased prevalence of classification of smallMIs as event, there is a lack of data on the association of LVH and CHD. In REGARDS, LVH derived from Cornell voltage criteria was a prognostic indicator of incident CHD in men, but not in women, with no evidence of racial differences. However, LVH was associated with increased overall mortality in AAs compared to whites, but with no gender differences [160]. REGARDS has also studied the ECG identification of LVH using a 7-lead approach [in which the precordial leads are replaced with a single mid-sternal chest lead (V), i.e., SV+RaVL] and the 12-lead Cornell voltage criteria [161]. LVH by the 12 lead approach was calculated as the sum of S wave in lead V3 (SV3) and R wave in lead aVL (RavL) [162]. Comparing the 7- to the 12-lead approach, no significant difference in terms of associations with demographics, LVH risk factors, and overall CHD mortality was observed [161]. Overall, the prevalence of LVH was greater in men using either approach [161]. These findings suggest that a seven-lead ECG technique might be used to detect LVH in large population studies.

Biases in Epidemiology Studies

In observational studies, knowing the risk status of participants could introduce bias during outcomes assessment [163, 164]. However, the extent of bias introduced by unblinded review of medical records during outcomes assessment remains unknown. This is important because blinding is labor intensive and costly. In REGARDS, for the predictors of race and geography, there was no evidence of bias in ascertaining CVoutcomes (i.e., chest pain MI, revascularization, and HF) from unblinded vs blinded medical record review [165]. Given the amount of resources (e.g., time and human expertise) required to maintain blinding, unblinded medical record review could be cost efficient when reviewing ubiquitous predictors such as race and geography.

In epidemiological studies involving disease-specific mortality, ascertaining the true cause of death from death certificates is often challenging since misclassification is well known [166]. In addition, the process of obtaining death certificates is often time consuming and resource intensive [166, 167], and there is lack of data on agreement between the cause of death provided by proxy, obtained from death certificates, or adjudicated by clinical experts. In REGARDS, there was a greater agreement between the proxy-reported and adjudicator-

determined cause of death when compared to the death certificate-reported cause. Compared to death certificates (with the gold standard adjudicator-determined cause of death), the proxy-reported cause of death had a greater sensitivity, specificity, and positive predictive value [168]. Thus, when determining the cause of death, obtaining information from a proxy may help save time, human labor, and financial resources.

In contrast to the cause of death, the extent of error with the subjective reporting of medical conditions such as obesity may lead to misclassification [169]. This was evident from discordance in the prevalence of obesity comparing self-reported obesity (i.e., by height and weight) as reported from the Behavioral Risk Factor Surveillance System (BRFSS), with directly measured obesity as assessed in REGARDS and NHANES [170–172]. There also may be differences in the magnitude of bias in self-reported height and weight that limits the use of these estimates (i.e., BRFSS) for comparisons across different geographical areas.

Use of Claims-Based Data

Data from health-care claims can be used to study medication effectiveness and to help design pharmacovigilance studies. Health-care claims-based algorithms have been used to predict high-risk populations for osteoporotic fracture [173], but their utility in predicting CHD risk remains unknown. Among REGARDS participants who were Medicare beneficiaries, a claims-based algorithm using 25 prespecified Medicare claim variables (e.g., demographics, CV risk, and health-care utilization factors) had a positive predictive value of 87 %, but only a 69 % sensitivity for identifying those at high risk for CHD events [174]. However, the claims-based algorithm lacks data on clinical and laboratory values; thus, it may be more sensitive in identifying people with diagnosed conditions than those with abnormal lab values. Generalizability needs to be considered in interpreting findings based on studies conducted to identify high-risk individuals using claimsbased algorithms. Further research is needed to develop algorithms that would comprehensively address laboratory values to identify patients at high risk of CV events.

Prevention and Quality of Care

A study comparing data from the Atherosclerosis Risk in Communities (ARIC) study, the Cardiovascular Health Study (CHS), and REGARDS suggests that after adjusting for changes in risk factor prevalence and the use of preventive medicines, out-of-hospital fatal CHD rates did not improve over time among middle-aged adults and increased among older adults (Table 10) [9, 175, 176]. These studies indicate that much work remains to be done to improve this situation.

The current guidelines for patients with stable CHD recommend intensive risk factor management and anti-ischemic therapies [177]. Recent analyses determined the proportion of REGARDS participants with CAD who achieved optimal risk factor goals as specified in the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial [i.e., aspirin use, nonsmoking, exercise ≥4 days/week, fasting glucose <126 mg/dL, body mass index <25 kg/m^2, low-density lipoprotein cholesterol <85 mg/dL, high-density lipoprotein cholesterol <40 mg/dL and triglyceride <150 mg/dL, SBP <130 mmHg and DBP <85 mmHg (<85 mmHg in DM] [178, 179]. The median number of goals

met was 4, and <25 % of participants achieved 5 or more goals. Older age, white race, higher income and education, and physical functioning were associated with meeting more goals. Therefore, there is a continuing need for improvement in risk factor management and preventive measures, and it is not clear which risk factor modifications, if sustained, would reduce recurrent CHD and CHD mortality. This issue was evaluated in REGARDS, and it was found that CHD risk was lower in those with certain (i.e., nonsmoking and physical activity) but no other (Mediterranean diet and waist circumference <88 cm in women and <102 cm in men) ideal lifestyle factors [179]. A greater number of ideal lifestyle factors were associated with lower recurrent CHD and mortality.

Statins have been used for both primary and secondary prevention of CVD [180, 181]. The increased CHD-related mortality in the stroke belt region of the USA could possibly be due to a lack of use of preventive medicines such as aspirin or statins. As shown in the ARIC study, routine use of aspirin was greater in regions outside of stroke belt [182]. However, in REGARDS, aspirin use was 6–10 % higher inside vs outside the stroke belt region [133], but significantly lower among AAs compared to whites (27 vs 35 %, respectively) [183•]. These findings suggest that, although regional disparity may not contribute towards higher CHD risk, racial disparity might. The findings in REGARDS of racial disparity in aspirin use are consistent with previous studies, but REGA RDS had a greater sample size of biracial national cohort. [182, 184]

The Justification of the Use of Statin in Primary Prevention: an Intervention Trial Using Rosuvastatin (JUPITER) trial reported that nondiabetic individuals who were not eligible for lipid lowering therapy (by virtue of normal LDL-C) but who had hsCRP levels ≥2 mg/L had reduced adverse vascular events and cardiovascular mortality when treated with rosuvastatin [185]. Applying the JUPITER criteria to REGA RDS participants without diabetes, 21 % were eligible for statins compared to 12 % when applying ATP III guidelines [186]. In REGARDS, those who were eligible for lipid lowering therapy using ATP III guidelines had a higher mortality compared to those eligible using JUPITER criteria [186]. In REGARDS, statin use was associated with lower levels of hsCRP and that the combined use of both statin and aspirin has a synergistic effect in reducing hsCRP levels highlighting the importance of using statins and aspirin for CHD prevention [187].

The 2013 Kidney Disease Improving Global Outcomes (KDIGO) clinical practice guidelines recommend statin use for all adults ≥50 years with CKD and not on dialysis [188]. However, the American College of Cardiology/American Heart Association (ACC/AHA) 2013 cholesterol treatment guidelines did not consider CKD as a deciding factor for statin initiation [189]. In REGARDS, only 50%of participants with CKD not on dialysis were taking statins. According to AHA/ ACC 2013 guidelines, 92 % of participants 50–79 years old with CKD not on dialysis were taking a statin or were eligible for statin therapy [190]. These findings suggest high concordance between 2013 KDIGO and AHA/ACC guidelines for statin initiation.

Statin use has been inconsistently linked with cognitive and memory impairment [191, 192]. A REGARDS study examined cognitive function using the Six-Item Screener [193] among statin and nonstatin users [194]. The results demonstrated that the proportion of participants

receiving a statin was similar in and out of the stroke belt, and there was no significant difference in cognitive impairment among statin users vs nonusers (8.7 vs 7.7 %) or among individuals living in the stroke belt vs other regions. These findings should help direct further research to clarify the controversy surrounding the effect of statin use on cognition [195, 196]. Despite existing guidelines, many patients with CHD or CV risk factors are untreated or undertreated [197, 198]. For example, in REGARDS, only 58.4 % of participants with CHD were on statins. Statin use among those with stroke or abdominal aortic aneurysm, diabetes, and a 10-year Framingham risk score >20 % was 41.2, 40.4, and 20.1 %, respectively. In addition, comparing those with CHD, participants with a FRS >20 % were less likely to have LDL-C <100 mg/dL [199]. These findings highlight the continuing need for increased awareness among the health-care providers to identify and treat high-risk populations.

In addition to these studies examining quality of care, REGARDS has contributed to the literature on regional level variations in CVD and CVD outcomes and the role of CHD risk factors. In REGARDS, a modest association between Framingham CHD Risk Score and CHD mortality (calculated using vital statistics obtained from Centers for Disease Control and Prevention) was observed across geographic regions [200]. However, a similar relationship was not demonstrated between stroke-related risk factors and mortality (i.e., the same state which had a higher incidence of CHD morality did not necessarily have a higher incidence of stroke mortality).These findings might be surprising given the strong association between CHD and stroke risk scores. However, differences in the scores exist (e.g., the Framingham CHD risk score does not take into account obesity as a risk factor) [201]. There is need for better understanding of mechanisms leading to such findings.

Future Directions

The lack of progress on minimizing incident acute CHD death demonstrates the need for further research that would help develop interventions to target-specific high-risk populations for better CHD outcomes. Studies that identify individuals well in advance of their mortal event to permit initiation of preventive interventions should be prioritized. REGARDS has addressed gender and racial disparities in the management of chronic diseases and has focused attention on the mechanisms associated with aTRH, depression, and increased risk for CHD and CHF in association with impaired cognition. All these areas need further investigation, such as studies of race–sex subgroups that will be made possible as additional events accrue. REGARDS has demonstrated that the epidemiology of MI is changing, coining the concept of “microsize” MI, a newly recognized and large proportion of contemporary MI events. Consistent clinical recognition of such microsize MI events and the quality of guideline concordant care received by patients suffering such events needs further investigation. Additionally, in light of the growing enthusiasm to use claims-based data to replace event adjudication, studies from REGA RDS have begun to provide important insights into the strengths and limitations of this approach. Further studies that examine the sensitivity and specificity of claims-based approaches to detecting contemporary MI events, especially in light of microsize MI, which was not detectable when claims-based algorithms were validated are needed. In conclusion, REGARDS has provided valuable insights into our understanding of the association between CHD and geographic,

racial and gender disparities, psychosocial and socioeconomic factors, comorbidities, behavioral factors, and lifestyle factors. There is a continued need to address lifestyle and behavioral factors to control modifiable CVrisk factors such as hypertension, hyperlipidemia, diabetes, and obesity, and to improve medication compliance among high-risk populations. The findings from REGARDS will continue to accrue, building the knowledge base to support the elimination of CHD disparities between AAs and whites while reducing CHD for all Americans. Finally, REGARDS is an observational study, and clinical trials are needed to confirm the findings applicable to the general population.

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Table 1

Outline of topics related to CHD

1	Incidence
2	Risk factors
	1. Blood pressure
	a. Prehypertension
	b. Medication nonadherence
	c. Psychosocial, behavioral, and environmental factors
	d. Apparent treatment resistant hypertension
	e. Pulse pressure
	2. Prediabetes and diabetes
	3. Dyslipidemia
	4. Diet and obesity
	5. Nontraditional risk factors
	a. Chronic kidney disease
	b. Atrial fibrillation with or without chronic kidney disease
	c. Depression and psychosocial factors
	d. High sensitivity C-reactive protein
3	Heart failure and cognition
4	Methodologic considerations
	a. Unrecognized myocardial infarction
	b. Troponin assays
	c. Electrocardiographic parameters
	d. Biases in epidemiological studies
	e. Use of claims-based data
5	Prevention and quality of care
6	Future directions

Table 2

Incidence

REGARDS reference—author	Year	Topic
[6]—Shuaib et al.	2012	Geographical distribution of CHD mortality in USA
[7••]—Safford et al.	2012	Racial and gender disparities in risk factors and incidence of CHD

Table 3

Blood pressure

REGARDS reference—author	Year	Topic
[15]—Glasser et al.	2011	Prevalence of prehypertension and risk factors.
[16]—Judd et al.	2011	Alcohol consumption and hypertension
[17]—Glasser et al.	2013	Prehypertension and CHD incidence
[23]—Banach et al.	2014	Medication adherence and cardiovascular mortality
[26]—Cummings et al.	2013	Medication nonadherence and BP control
[27•]—Cummings et al.	2013	Access to generic medications and BP control
[29]—Cummings et al.	2010	Racial disparities in BP control
[30]—Safford et al.	2007	Treatment disparities between AAs and whites
[33]—Durrant et al.	2010	BP control and trust in physicians
[35]—Durrant et al.	2012	Awareness and treatment of hypertension in health professional shortage areas
[36]—Howard et al.	2006	Racial disparities in awareness and treatment of hypertension
[39]—Kent et al.	2011	Environmental influence on BP control
[42]—Levine et al.	2011	Waist circumference and BP control
[46]—Muntner et al.	2010	Antihypertensive medication adherence in chronic kidney disease
[48]—Irvin et al.	2014	aTRH and CHD risk
[49]—Irvin et al.	2012	Medication nonadherence and pseudoresistant hypertension
[53]—Tanner et al.	2014	aTRH and end stage renal disease
[55]—Calhoun et al.	2014	Refractory hypertension and lack of optimal medication regimen
[58]—Diaz et al.	2014	Healthy life style factors and cardiovascular events
[59]—Shimbo et al.	2013	Unhealthy life style risk factors and number of antihypertensive medications
[65]—Glasser et al.	2014	Pulse pressure and CHD risk

Table 4

Prediabetes and diabetes

REGARDS reference—author	Year	Topic
[6]—Shuaib et al.	2012	Awareness, treatment and control of diabetes
[69]—Lee L et al.	2014	Prevalence of prediabetes by region and race
[71]—Carson	2014	Diabetes and CHD incidence

Table 5

Dyslipidemia

REGARDS reference—author	Year	Topic
[6]—Shuaib et al.	2012	Awareness, treatment and control of diabetes
[69]—Lee L et al.	2014	Prevalence of prediabetes by region and race
[71]—Carson	2014	Diabetes and CHD incidence

Table 6

Diet and obesity

REGARDS reference—author	Year	Topic
[75]—Newby et al.	2009	Nutrient intakes by race
[78]—Kramer et al.	2011	BMI and risk of all-cause mortality
[79]—Lakoski et al.	2011	Waist circumference and all-cause mortality in AA
[83]—Brown et al.	2010	Applying International Diabetes Foundation and Adult Treatment Panel III criteria of metabolic syndrome

Table 7

Nontraditional risk factors

REGARDS reference—author	Year	Topic
[79]—Lakoski et al.	2011	Association between CRP and BMI
[87]—Gutierrez O et al.	2013	Urine albumin, urine albumin/creatinine ratio, and CHD
[91]—Muntner et al.	2013	Life's simple 7 risk factors and end stage renal disease
[94]—McClellan et al.	2009	CKD awareness in patients with CHD
[95]—Tuot et al.	2013	CKD awareness, healthy behavior and risk factor control
[98]—Chang et al.	2012	Medications for secondary prevention and CKD
[100]—Baber et al.	2011	Association of CKD and AF
[103]—Tanner et al.	2011	Metabolic syndrome and AF
[106]—Meschia et al.	2010	Awareness of AF and use of anticoagulation by race
[109]—Prineas et al.	2009	Methods used to detect AF
[110]—Soliman et al.	2014	AF and incident MI
[111]—Prineas et al.	2005	Prevalence of AF in stroke belt
[114]—Kronish et al.	2012	Depressive symptoms and adverse cardiovascular health
[115]—Ye et al.	2013	Depressive symptoms and the risk of MI and death
[120]—Haley et al.	2010	Caregiving stress and CHD risk
[121]—Redmond et al.	2013	Stress and incident CHD
[126••]—Brown et al.	2011	Lack of insurance and use of preventive medications or treatment

Table 8

Heart failure and cognition

REGARDS reference—author	Year	Topic
[135]—Pullicino et al.	2009	Association of HF with decreased BP and cerebral hypoperfusion
[137•]—Pullicino et al.	2008	HF and cognitive impairment in the presence of depression

Table 9

Methodologic considerations

REGARDS reference—author	Year	Topic
[7••]—Safford et al.	2012	Incidence of very small NSTEMIs and racial disparities
[142]—Rizk et al.	2012	UMI in the presence of CKD
[146]—Levitan et al.	2013	UMI and use of preventive medications
[148]—Levitan et al.	2013	Assessment tool to determine UMI
[152•]—Safford et al.	2013	Sensitivity of troponin assays and microsize MI
[157]—Prineas et al.	2012	Racial differences in ECG abnormalities
[160]—Prineas et al.	2014	LVH and risk of incident CHD
[161]—Soliman et al.	2010	Calculating Cornell voltage for LVH using non-standard chest electrode
[165]—Parmar et al.	2010	Unblinded medical record review and outcomes assessment
[168]—Halanych et al.	2011	Comparing proxy reported and adjudicated determined cause of death
[170]—Le et al.	2014	Comparing self-reported and directly measured obesity
[174]—Thacker et al.	2014	Use of claim based algorithms to identify CHD risk

Table 10

Prevention and quality of care

REGARDS reference—author	Year	Topic
[178]—Brown et al.	2014	Prevalence of optimal risk factor goal
[179]—	Booth et al.	2014 Ideal lifestyle factors and CHD risk
[183•]—Glasser et al.	2008	Aspirin use by race and geography
[186]—Cushman et al.	2010	Applying JUPITER and ATP III criteria for statin use
[187]—Fisher et al.	2008	Effect of aspirin and statin use on CRP
[190]—Colantonio et al.	2014	Contrasting cholesterol guidelines in CKD
[194]—Glasser et al.	2010	Association of statin use and cognitive performance
[199]—Gamboa et al.	2014	Statin use in the presence of CHD
[200]—Howard et al.	2009	Association between CHD risk scores and mortality