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# Risco Cardiovascular
# Outcomes Cardiovasculares

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# Risco Cardiovascular

Pesquisa Bibliográfica efectuada em Pubmed (www.ncbi.nlm.nih.gov/ - Jul a Set 2018

Tex Heart Inst J. 2018 Aug 1;45(4):205-213.

# High-Risk Cardiovascular Conditions in Sports-Related Sudden Death: Prevalence in 5,169 Schoolchildren Screened via Cardiac Magnetic Resonance.

Angelini P, Cheong BY, Lenge De Rosen VV, Lopez A, Uribe C, Masso AH, Ali SW, Davis BR, Muthupillai R, Willerson JT.

Improving preparticipation screening of candidates for sports necessitates establishing the prevalence of high-risk cardiovascular conditions (hr-CVC) that predispose young people to sudden cardiac death (SCD). Our accurate, novel protocol chiefly involved the use of cardiac magnetic resonance (CMR) to estimate this prevalence. Middle and high school students from a general United States population were screened by means of questionnaires, resting electrocardiograms, and CMR to determine the prevalence of 3 types of hr-CVC: electrocardiographic abnormalities, cardiomyopathies, and anomalous coronary artery origin from the opposite sinus with intramural coronary course (ACAOS-IM). We examined the range of normal left ventricular size and function in the main study cohort (schoolchildren 11-14 yr old). We defined diagnostic criteria for hr-CVC and compared the cardiac measurements of these younger participants with those of older children whom we examined (age, 15-18 yr). From 5,169 completed diagnostic studies (mean participant age, 13.06 ± 1.78 yr), CMR results revealed 76 previously undiagnosed cases of hr-CVC (1.47% of the total cohort): 11 of dilated cardiomyopathy (14.5%), 3 of nonobstructive hypertrophic cardiomyopathy (3.9%), 23 ACAOS-IM cases (30.3%; 6 left-ACAOS and 17 right-ACAOS), 4 Wolff-Parkinson-White patterns (5.3%), 34 prolonged QT intervals (44.7%), and 1 Brugada pattern (1.3%). Cardiomyopathies were significantly more prevalent in the older children. Of note, we identified 959 cases (18.5%) of left ventricular noncompaction. If our estimate is accurate, only 1.47% of school-age sports participants will need focused secondary evaluations; the rest can probably be reassured about their cardiac health after one 30-minute screening study.

PMCID: PMC6183627PMID: 30374227

J Am Heart Assoc. 2018 Aug 7;7(15):e009250.

# Life Course Trajectories of Cardiovascular Risk Factors in Women With and Without Hypertensive Disorders in First Pregnancy: The HUNT Study in Norway.

Haug EB, Horn J, Markovitz AR, Fraser A, Vatten LJ, Macdonald-Wallis C, Tilling K, Romundstad PR, Rich-Edwards JW, Åsvold BO.

Background: Women with hypertensive pregnancy disorders have adverse levels of cardiovascular risk factors. It is unclear how this adverse risk factor profile evolves during adult life. We compared life course trajectories of cardiovascular risk factors in women with preeclampsia or gestational hypertension in their first pregnancy to normotensive women.

Methods and Results: We linked information on cardiovascular risk factors from the population-based HUNT (Nord-Trøndelag Health Study) surveys with pregnancy information from the Medical Birth Registry of Norway. Trajectories of cardiovascular risk factors were constructed for 22 308 women with a normotensive first pregnancy; 1092 with preeclampsia, and 478 with gestational hypertension in first pregnancy. Already before first pregnancy, women with preeclampsia in their first pregnancy had higher measures of adiposity, blood pressure, heart rate, and serum lipids and glucose compared with women with a normotensive first pregnancy. After first pregnancy, there was a parallel development in cardiovascular risk factor levels, but women with a normotensive first pregnancy had a time lag of >10 years compared with the preeclampsia group. There were no clear differences in risk factor trajectories between women with gestational hypertension and women with preeclampsia.

Conclusions: Women with hypertensive pregnancy disorders in their first pregnancy had an adverse cardiovascular risk factor profile before pregnancy compared with normotensive women, and the differences persisted beyond 50 years of age. Hypertensive disorders in pregnancy signal long-term increases in modifiable cardiovascular risk factors, and may be used to identify women who would benefit from early prevention strategies.

PMCID: PMC6201453
PMID: 30371249

Circ Res. 2018 Sep 14;123(7):886-904.

## Age-Related Changes in Glucose Metabolism, Hyperglycemia, and Cardiovascular Risk.

Chia CW, Egan JM, Ferrucci L.

Aging and diabetes mellitus are 2 well-known risk factors for cardiovascular disease (CVD). During the past 50 years, there has been an dramatic increase in life expectancy with a simultaneous increase in the prevalence of diabetes mellitus in the older population. This large number of older individuals with
diabetes mellitus is problematic given that CVD risk associated with aging and diabetes mellitus. In this review, we summarize epidemiological data relating to diabetes mellitus and CVD, with an emphasis on the aging population. We then present data on hyperglycemia as a risk factor for CVD and review the current knowledge of age-related changes in glucose metabolism. Next, we review the role of obesity in the pathogenesis of age-related glucose dysregulation, followed by a summary of the results from major randomized controlled trials that focus on cardiovascular risk reduction through glycemic control, with a special emphasis on older adults. We then conclude with our proposed model of aging that body composition changes and insulin resistance link possible dysregulation of physiological pathways leading to obesity and diabetes mellitus-both forms of accelerated aging-and risks for CVD.

PMCID: PMC6205735 [Available on 2019-09-14]
PMID: 30355075

Hypertension. 2018 Sep;72(3):602-609.

## Prevalence of Hypertension and Cardiovascular Risk According to Blood Pressure Thresholds Used for Diagnosis.

Lamprea-Montealegre JA, Zelnick LR, Hall YN, Bansal N, de Boer IH.

We sought to estimate the prevalence of hypertension and characteristics of hypertensive adults in the United States according to blood pressure (BP) thresholds used for diagnosis and estimate their associated cardiovascular disease risk. Analyses included adults 20 years of age or older in the 2013 to 2014 National Health and Nutrition Examination Survey (N=5389) and enrolled participants in SPRINT (Systolic Blood Pressure Intervention Trial; N=9361) and the ACCORD-BP trial (Action to Control Cardiovascular Risk in Diabetes-Blood Pressure; N=4733). In the National Health and Nutrition Examination Survey, prevalence estimates incorporated the probability of observing elevated BP on 2 separate occasions. Using the new BP thresholds of ≥130/80 mmHg, ≈24 million new American adults would be diagnosed as having hypertension and 4.3 million would be recommended to start antihypertensive medications. These individuals would have a lower mean atherosclerotic cardiovascular disease risk (17%) than participants in SPRINT and ACCORD-BP (22% and 27%) and would be less likely to have prevalent cardiovascular disease (9% versus 17% and 34%). In SPRINT and ACCORD-BP, only a minority (9% and 13%) of participants were not on antihypertensive medications at baseline, and rates of incident cardiovascular disease in these participants were substantially lower compared with those on baseline BP medications. We conclude that adopting the American College of Cardiology/American Heart Association guidelines would lead to a substantial increase in the prevalence of hypertension and in the number of American adults recommended to start antihypertensive medications. These individuals would have a substantially lower cardiovascular risk than most participants previously studied in 2 large BP trials.

PMCID: PMC6205214 [Available on 2019-09-01]
PMID: 30354757

Circ Genom Precis Med. 2018 Aug;11(8):e002146.

## Healthcare Utilization and Patients' Perspectives After Receiving a Positive Genetic Test for Familial Hypercholesterolemia.

Jones LK, Kulchak Rahm A, Manickam K, Butry L, Lazzeri A, Corcoran T, Komar D, Josyula NS, Pendergrass SA, Sturm AC, Murray MF.

BACKGROUND: The MyCode Community Health Initiative (MyCode) is returning actionable results from whole exome sequencing. Familial hypercholesterolemia (FH) is an inherited condition characterized by premature cardiovascular disease.
METHODS: We used multiple methods to assess care in 28 MyCode participants who received FH results. Chart reviews were conducted on 23 individuals in the sample and 7 individuals participated semistructured interviews.
RESULTS: Chart reviews for 23 individuals with a Geisinger primary care provider found that 4 individuals (17% of 23) were at LDL-C (low-density lipoprotein cholesterol) goal (of either LDL-C <100 mg/dL for primary prevention and LDL-C <70 mg/dL for secondary prevention) and 17 individuals (74% of 23) were prescribed lipid-lowering therapy before genetic result disclosure. After disclosure of the genetic test result, 5 individuals (22% of 23) met their LDL-C goal and 18 individuals (78% of 23) were prescribed lipid-lowering therapy. Follow-up care about this result was not documented for 4 individuals (17% of 23). Changes to intensity of medication management were made for 8 individuals (47% of 17 individuals previously prescribed lipid-lowering therapy). Interviewed individuals (n=7) were not surprised by their result as all knew they had high cholesterol; however, individuals did not seem to discern FH as a separate condition from their high cholesterol.
CONCLUSIONS: Among individuals receiving genetic diagnosis of FH, >25% had no changes to lipid-lowering therapy, despite not being at LDL-C goal and learning their high cholesterol is related to a genetic condition requiring more aggressive treatment. Individuals and clinicians may have an inadequate understanding of FH as a distinct condition requiring enhanced medical management.

PMID: 30354341

Curr Probl Cardiol. 2018 Sep 20. pii: S0146-2806(18)30142-7.

## Gender Identity, Hormone Therapy, and Cardiovascular Disease Risk.

Martinez C, Rikhi R, Haque T, Fazal A, Kolber M, Hurwitz BE, Schneiderman N, Brown TT.

Transgender individuals represent a medically underserved and under researched population. There is a growing number of studies illustrating the importance of hormone therapy treatments in transgender men and women to assist ameliorating gender dysphoria and promoting well-being. However, the cardiovascular effects of these hormones are controversial. Large longitudinal epidemiological studies of cardiovascular event outcomes in these populations do not exist. In addition, studies of cardiovascular complications of transgender hormone therapy are limited in number and complicated by poor control of medication regimen, presence of gender confirming surgery, use of prescribed medications for prevailing conditions, and alcohol, smoking or illicit substance use, and comorbidities, such as HIV infection. The following provides an overview of current guidelines for hormone therapy regimens used by transgender individuals, as well as what is known about the use of exogenous hormones on the cardiovascular system and cardiovascular disease risk. Several gaps in our understanding of the cardiovascular effects of endogenous and exogenous hormones in treated transgender individuals are identified, which provide direction for future study.

PMID: 30340769

J Clin Lipidol. 2018 Sep 11. pii: S1933-2874(18)30371-4

## Lipoprotein(a) and secondary prevention of atherothrombotic events: A critical appraisal.

Boffa MB, Stranges S, Klar N, Moriarty PM, Watts GF, Koschinsky ML

Elevated plasma concentrations of lipoprotein(a) [Lp(a)] are an independent, and possibly causal, risk factor for atherothrombotic diseases including coronary heart disease. The principal evidence base for this comes from large population studies focusing on first atherothrombotic events. However, inconsistent findings have been reported from studies investigating the impact of elevated Lp(a) on atherothrombotic events in subjects with preexisting cardiovascular disease. This question is very important because the secondary prevention population is recommended for Lp(a) screening by some guidelines and could be an important target group for Lp(a)-lowering therapies that are currently on the horizon. In this review, we survey the secondary prevention literature as it relates to Lp(a) and identify some possible confounding factors that may underlie the inconsistent findings, such as index event bias.

PMID: 30316749

Am J Cardiol. 2018 Sep 13. pii: S0002-9149(18)31751-X.

## Acute and Subacute Triggers of Cardiovascular Events.

Schwartz BG, Kloner RA, Naghavi M.

Inability to predict short-term cardiovascular (CV) events and take immediate preemptive actions has long been the Achilles heel of cardiology. However, certain triggers of these events have come to light. Although these triggers are nonspecific and are part of normal life, studying their temporal relationship with the onset of CV events provides an opportunity to alert high-risk atherosclerotic patients who may be most vulnerable to such triggers, the "vulnerable patient". Herein, we review the literature and shed light on the epidemiology and underlying pathophysiology of different triggers. We describe that certain adrenergic triggers can precipitate a CV event within minutes or hours; whereas triggers that elicit an immune or inflammatory response such as infections may tip an asymptomatic "vulnerable patient" to become symptomatic days and weeks later. In conclusion, healthcare providers should counsel high-risk CV patients (e.g., in secondary prevention clinics or those with coronary artery Calcium >75th percentile) on the topic, advise them to avoid such triggers, take protective measures once exposed, and seek emergency care immediately after becoming symptomatic after such triggers. Furthermore, clinical trials targeting triggers (prevention or intervention) are needed.

PMID: 30309628

Curr Treat Options Cardiovasc Med. 2018 Sep 26;20(11):89.

## Coronary Artery Calcium: Recommendations for Risk Assessment in Cardiovascular Prevention Guidelines.

Al Rifai M, Cainzos-Achirica M, Kianoush S, Mirbolouk M, Peng A, Comin-Colet J, Blaha MJ.

Erratum in
Curr Treat Options Cardiovasc Med. 2018 Oct 18;20(11):92.

PURPOSE OF REVIEW: In this review, we evaluate the coronary artery calcium (CAC) score as a biomarker for advanced atherosclerotic cardiovascular disease (ASCVD) risk assessment.
RECENT FINDINGS: We summarize the evidence from multiple epidemiological studies, which show a clear advantage of CAC compared to traditional and non-traditional cardiovascular risk factors. We then compare the recommendations included in the 2013 American College of Cardiology/American Heart Association (ACC/AHA) and in the 2017 Society of Cardiovascular Computed Tomography (SCCT) guidelines for the use of CAC in ASCVD risk assessment, and examine the recent 2018 US Preventive Services Task Force (USPSTF) document. Finally, based on the currently available evidence, we provide constructive input for the upcoming ACC/AHA guidelines, regarding the population in whom CAC is most likely to be informative, the level of evidence that we believe should be assigned to CAC as an advanced ASCVD risk assessment tool, and the special populations in whom CAC might be beneficial for further risk assessment. We support a pragmatic approach that combines the pooled cohort equations (PCE) for initial ASCVD risk stratification, followed by CAC for refining ASCVD risk assessment among a broad range of intermediate risk patients and other special groups.

PMID: 30255362

Liver Int. 2018 Sep 25. doi: 10.1111/liv.13973. [Epub ahead of print]

## Cardiovascular risk factors in non-alcoholic fatty liver disease.

Hagström H, Nasr P, Ekstedt M, Hammar U, Stål P, Askling J, Hultcrantz R, Kechagias S.

BACKGROUND & AIMS: Patients with non-alcoholic fatty liver disease (NAFLD) are at an increased risk for cardiovascular disease (CVD). It is unclear whether histological variables may help predict CVD risk. We evaluated histology and traditional CV risk factors as predictors of CVD outcomes in a large NAFLD cohort.
METHODS: We included 603 biopsy-proven NAFLD patients free of baseline CVD and matched these (1:10, by age, sex and municipality) to 6269 population controls. All individuals were cross-linked to national registries to ascertain incident CVD events, defined as acute ischaemic heart disease or stroke. The presence of CV risk factors and liver histology were available in NAFLD patients only. Cox regression models were used to estimate hazard ratios (HR) for incident CVD.
RESULTS: During a mean follow-up of 18.6 years, 168 (28%) of NAFLD patients and 1325 (21%) of controls experienced a CVD event (HR 1.54, 95%CI 1.30-1.83). Within the NAFLD cohort, age, male sex, type 2 diabetes, smoking and triglycerides were associated with risk of CVD. Taking these CV risk factors into account, no histological parameter, including presence of NASH and fibrosis stage, were associated with incident CVD.
CONCLUSIONS: Patients with NAFLD are at an increased risk for CVD compared to matched controls, but histological parameters do not seem to independently predict this risk.

PMID: 30253056

J Infect Dis. 2018 Sep 22;218(suppl_2):S102-S106.

## Herpes Zoster: Epidemiological Links With Stroke and Myocardial Infarction.

Warren-Gash C.

Routine data from electronic health records (EHRs) provide insights into links between herpes zoster (HZ) and cardiovascular complications such as stroke or myocardial infarction (MI) in different populations worldwide. Evidence from large EHR studies using both self-controlled case series and traditional cohort designs suggests that there is a transient increase in the risk of stroke after HZ, which gradually resolves over 6-12 months. In these studies, herpes zoster ophthalmicus was associated with a higher risk of stroke than HZ at other sites. A larger effect size was seen in people aged under 40 years. Existing studies also suggest that HZ may have a triggering effect on MI, although fewer studies examined this outcome. Further evidence is needed on the effectiveness and cost-effectiveness of vaccine and antiviral drugs to reduce cardiovascular complications after HZ from studies that are designed to minimize selection biases and confounding by indication.

PMID: 30247593

Am J Epidemiol. 2018 Sep 15. [Epub ahead of print]

# The Origins and Early Evolution of Epidemiologic Research in Cardiovascular Diseases (CVD): A Tabular Record of Cohort and Case-Control Studies and Preventive Trials Initiated from 1946-1976.

Blackburn H.

This article provides a ready reference to the pioneering formal studies in CVD epidemiology during three decades of its evolution into an established academic field making contributions to the public health. The article is not intended to be a history of CVD epidemiology nor an editorial about its significance. The appended tables include the title and starting date of the early studies, the name of their principal investigator, and reference to a single defining article from each. The early observational studies of CVD epidemiology provided a widely useful CVD risk-factor paradigm. The early clinical trials justified the more definitive preventive trials of the 1980s and beyond. These early researches in populations, along with others in the clinic and laboratory, led to greater understanding of the causes of CVD, to a vigorous practice of preventive cardiology, and to national policy and programs of health promotion, all coincident with a 50-year decline in CVD mortality rates.

PMID: 30239595

Clin Investig Arterioscler. 2018 Sep 17. pii: S0214-9168(18)30083-4.

# Document of recommendations of the SEA 2018. Lifestyle in cardiovascular prevention.

[Article in English, Spanish]

Pérez-Jiménez F, Pascual V, Meco JF, Pérez Martínez P, Delgado Lista J, Domenech M, Estruch R, León-Acuña A, López-Miranda J, Sánchez-Ramos A, Soler I Ferrer C, Soler-Rivas C, Solá Alberich RM, Valdivielso P, Ros E.

Lifestyle is a complex concept that includes aspects external to ourselves that can modulate and influence our health. The knowledge of the relationship between lifestyle and cardiovascular risk does not attain the level of evidence achieved with clinical trials with drugs, because clinical studies are scarce and mainly of observational nature, albeit based on large cohorts. Nutritional epidemiology has the added difficulty of being based mostly on subjective dietary recall methods to ascertain nutrient and food intake over time, with the additional problems of incomplete data collection, variable measurements of adherence due to seasonal and geographical differences in food composition, and the changing eating behavior that human beings have over time. The purpose of this document is to carry out an updated and hierarchical review of the relationship between lifestyle and cardiovascular disease based on current evidence, paying attention to three aspects that are of great pathogenic importance and are directly modifiable: physical activity, tobacco consumption, and diet. With this, we intend to update the knowledge on this relationship, construct evidence-based recommendations, and provide a simple tool for clinical practice especially directed to health professionals involved in the care of people at cardiovascular risk, defining simple and easy strategies for individuals who receive advice for the primary and secondary prevention of cardiovascular diseases.

PMID: 30236615

Atherosclerosis. 2018 Sep 8;278:1-6

## Prediabetes and cardiovascular disease risk: A nested case-control study.

Hu H, Mizoue T, Sasaki N, Ogasawara T, Tomita K, Nagahama S, Hori A, Nishihara A, Imai T, Yamamoto M, Eguchi M, Kochi T, Miyamoto T, Honda T, Nakagawa T, Yamamoto S, Okazaki H, Uehara A, Shimizu M, Murakami T, Kuwahara K, Nanri A, Konishi M, Kabe I, Dohi S; Japan Epidemiology Collaboration on Occupational Health Study Group.

BACKGROUND AND AIMS: We aimed to examine the risk of cardiovascular disease (CVD) with persistent prediabetes during the last four years prior to a CVD event in a large occupational cohort in Japan.
METHODS: We performed a nested case-control study using data from the Japan Epidemiology Collaboration on Occupational Health Study. A total of 197 registered cases of CVD were identified and matched individually with 985 controls according to age, sex, and worksite. Prediabetes was defined as fasting plasma glucose 100-125 mg/dL and/or HbA1c 5.7-6.4%. Persistent prediabetes was defined as having prediabetes at years one and four prior to the onset/index date; persistent normoglycemia was similarly defined. Associations between prediabetes and CVD risk were assessed using conditional logistic regression models.
RESULTS: Compared with people with persistent normoglycemia over the four years prior to the onset/index date, the unadjusted odds ratio (95% confidence interval) for CVD was 2.88 (1.56, 5.32) for people with persistent prediabetes. After adjusting for BMI, smoking, hypertension, and dyslipidemia assessed four years before the onset/index date, the association was slightly attenuated to an OR (95% confidence interval) of 2.62 (1.31, 5.25). Prediabetes assessed at single time points was also associated with an elevated risk of CVD, with multivariable-adjusted odds ratio (95% confidence interval) of 1.72 (1.12, 2.64) and 2.13 (1.32, 3.43) for prediabetes at one and four years prior to the onset/index date, respectively.
CONCLUSIONS: Prediabetes is associated with an increased risk of CVD. Identification and management of prediabetes are important for the prevention of CVD.

PMID: 30227266

Diabetes Obes Metab. 2018 Sep 17. doi: 10.1111/dom.13537. [Epub ahead of print]

# Increased residual cardiovascular risk in patients with diabetes and high versus normal triglycerides despite statin-controlled LDL cholesterol.

Nichols GA, Philip S, Reynolds K, Granowitz CB, Fazio S.

AIM: To determine whether high triglycerides (TG) in the presence of statin-controlled LDL-C influence the risk of cardiovascular disease (CVD) among patients with diabetes in real-world clinical practice.

MATERIALS AND METHODS: We identified adults with diabetes from the Southern California and Pacific Northwest regions of Kaiser Permanente. We included patients undergoing statin therapy with LDL-C from 40-100 mg/dL who were not undergoing other lipid-lowering therapies and had a prior diagnosis of atherosclerotic CVD or at least one other CVD risk factor. We grouped patients into high TG (200-499 mg/dL; n = 5542) or normal TG (<150 mg/dL, n = 22 411) from January 2010 through December 2016 to compare incidence rates and rate ratios of first non-fatal myocardial infarction (MI), non-fatal stroke, unstable angina and coronary revascularization. We adjusted multivariable analyses for age, sex, race/ethnicity, smoking status, blood pressure, HbA1c, serum creatinine, presence of ischaemic heart disease and study site.

RESULTS: Adjusted rate ratios for the four outcomes were all statistically significantly different. The incidence rate for non-fatal MI was 30% higher in the high TG group (rate ratio, 1.30; 95% CI, 1.08-1.58; P = 0.006). The rate was 23% higher for non-fatal stroke (1.23, 1.01-1.49, P = 0.037), 21% higher for coronary revascularization (rate ratio, 1.21; 95% CI, 1.02-1.43; P = 0.027) and was, non-significantly, 33% higher for unstable angina (rate ratio, 1.33; 95% CI, 0.87-2.03; P = 0.185).

CONCLUSIONS: Despite statin-controlled LDL-C levels, CV events were greater among patients with diabetes and high TG levels. Because we controlled for cardiometabolic risk factors, it is likely that the difference in TG levels contributed to the excess risk observed in patients with high TGs.

PMID: 30225881

Psychol Med. 2018 Sep 17:1-11.

# Combined influence of depressive symptoms and systemic inflammation on all-cause and cardiovascular mortality: evidence for differential effects by gender in the English Longitudinal Study of Ageing.

Lawes S, Demakakos P, Steptoe A, Lewis G, Carvalho LA.

BACKGROUND: Depressive symptoms and inflammation are risk factors for cardiovascular disease (CVD) and mortality. We investigated the combined association of these factors with the prediction of CVD and all-cause mortality in a representative cohort of older men and women.

METHODS: We measured C-reactive protein (CRP) and depressive symptoms in 5328 men and women aged 52-89 years in the English Longitudinal Study of Ageing. Depressive symptoms were measured using the eight-item Centre for Epidemiological Studies Depression Scale. CRP was analysed from peripheral blood. Mortality was ascertained from national registers and associations with depressive symptoms and inflammation were estimated using Cox proportional hazard models.

RESULTS: We identified 112 CVD related deaths out of 420 all-cause deaths in men and 109 CVD related deaths out of 334 all-cause deaths in women over a mean follow-up of 7.7 years. Men with both depressive symptoms and high CRP (3-20 mg/L) had an increased risk of CVD mortality (hazard ratio; 95% confidence interval: 3.89; 2.04-7.44) and all-cause mortality (2.40; 1.65-3.48) after adjusting for age, socioeconomic variables and health behaviours. This considerably exceeds the risks associated with high CRP alone (CVD 2.43; 1.59-3.71, all-cause 1.49; 1.20-1.84). There was no significant increase in mortality risk associated with depressive symptoms alone in men. In women, neither depressive symptoms or inflammation alone or the combination of both significantly predicted CVD or all-cause mortality.

CONCLUSIONS: The combination of depressive symptoms and increased inflammation confers a considerable increase in CVD mortality risk for men. These effects appear to be independent, suggesting an additive role.

PMID: 30220259

Nutrients. 2018 Sep 5;10(9). pii: E1237.

## Moderate Beer Intake and Cardiovascular Health in Overweight Individuals.

Padro T, Muñoz-García N, Vilahur G, Chagas P, Deyà A, Antonijoan RM, Badimon L.

Consistent epidemiological evidence indicates that low-to-moderate alcohol consumption is inversely associated with cardiovascular event presentation, while high levels of alcohol intake are associated to increased cardiovascular risk. Little is known on the effects of moderate beer intake in the metabolic syndrome. The aim of this study is to investigate the effects of moderate and regular daily intake of beer with meals in overweight (body mass index (BMI) of 28⁻29.9 kg/m²) or obese class 1 (BMI of 30⁻35 kg/m²) individuals without other cardiovascular risk factors (dyslipidemia, type 2-diabetes, hypertension) focusing on the effects related to changes in weight, in lipoproteins and vascular endothelial function. We have performed an open, prospective two-arms longitudinal crossover study to investigate the effects associated with regular consumption (four week) of alcohol-free-beer (0 g alcohol/day) or traditional-beer (30 g alcohol/day in men and 15 g alcohol/day in women) on anthropometrical and biochemical parameters, liver and kidney function biomarkers, and vascular endothelial function. After four-week intervention with traditional and/or alcohol-free beer, BMI did not show any significant change and values for liver and kidney functions were within the normal levels. Moderate traditional beer intake did not affect lipid levels-however it significantly increased the antioxidant capacity of high density lipoprotein (HDL). In addition, apoB-depleted serum (after the four-week intervention period) showed a higher potential to promote cholesterol efflux from macrophages. Beer consumption did not induce vascular endothelial dysfunction or stiffness. In summary, our results based on a 12-week prospective study provide evidence that moderate intake of beer (traditional and alcohol-free) does not exert vascular detrimental effects nor increases body weight in obese healthy individuals. In contrast, moderate intake of beer increases the anti-oxidative properties of HDL and facilitates cholesterol efflux, which may prevent lipid deposition in the vessel wall.

PMCID: PMC6164820
PMID: 30189619

BMC Cardiovasc Disord. 2018 Sep 4;18(1):180.

## Mortality and cardiovascular disease burden of uncontrolled diabetes in a registry-based cohort: the ESCARVAL-risk study.

Navarro-Pérez J, Orozco-Beltran D, Gil-Guillen V, Pallares V, Valls F, Fernandez A, Perez-Navarro AM, Sanchis C, Dominguez-Lucas A, Martin-Moreno JM, Redon J, Tellez-Plaza M; ESCARVAL STUDY GROUP.

BACKGROUND: Despite the epidemiological evidence about the relationship between diabetes, mortality and cardiovascular disease, information about the population impact of uncontrolled diabetes is scarce. We aimed to estimate the attributable risk associated with HbA1c levels for all-cause mortality and cardiovascular hospitalization.
METHODS: Prospective study of subjects with diabetes mellitus using electronic health records from the universal public health system in the Valencian Community, Spain 2008-2012. We included 19,140 men and women aged 30 years or older with diabetes who underwent routine health examinations in primary care.
RESULTS: A total of 11,003 (57%) patients had uncontrolled diabetes defined as HbA1c ≥6.5%, and, among those, 5325 participants had HbA1c ≥7.5%. During an average follow-up time of 3.3 years, 499 deaths, 912 hospitalizations for coronary heart disease (CHD) and 786 hospitalizations for stroke were recorded. We observed a linear and increasingly positive dose-response of HbA1c levels and CHD hospitalization. The relative risk for all-cause mortality and CHD and stroke hospitalization comparing patients with and without uncontrolled diabetes was 1.29 (95 CI 1.08,1.55), 1.38 (95 CI 1.20,1.59) and 1.05 (95 CI 0.91, 1.21), respectively. The population attributable risk (PAR) associated with uncontrolled diabetes was 13.6% (95% CI; 4.0-23.9) for all-cause mortality, 17.9% (95% CI; 10.5-25.2) for CHD and 2.7% (95% CI; -5.5-10.8) for stroke hospitalization.
CONCLUSIONS: In a large general-practice cohort of patients with diabetes, uncontrolled glucose levels were associated with a substantial mortality and cardiovascular disease burden.

PMCID: PMC6122181
PMID: 30176799

BMJ. 2018 Aug 29;362:k3310.

## Environmental toxic metal contaminants and risk of cardiovascular disease: systematic review and meta-analysis.

Chowdhury R, Ramond A, O'Keeffe LM, Shahzad S, Kunutsor SK, Muka T, Gregson J, Willeit P, Warnakula S, Khan H, Chowdhury S, Gobin R, Franco OH, Di Angelantonio E.

OBJECTIVE: To conduct a systematic review and meta-analysis of epidemiological studies investigating the association of arsenic, lead, cadmium, mercury, and copper with cardiovascular disease. DESIGN: Systematic review and meta-analysis.
DATA SOURCES: PubMed, Embase, and Web of Science searched up to December 2017.
REVIEW METHODS: Studies reporting risk estimates for total cardiovascular disease, coronary heart disease, and stroke for levels of arsenic, lead, cadmium, mercury, or copper were included. Two investigators independently extracted information on study characteristics and outcomes in accordance with PRISMA and MOOSE guidelines. Relative risks were standardised to a common scale and pooled across studies for each marker using random effects meta-analyses.
RESULTS: The review identified 37 unique studies comprising 348259 non-overlapping participants, with 13033 coronary heart disease, 4205 stroke, and 15274 cardiovascular disease outcomes in aggregate. Comparing top versus bottom thirds of baseline levels, pooled relative risks for arsenic and lead were 1.30 (95% confidence interval 1.04 to 1.63) and 1.43 (1.16 to 1.76) for cardiovascular disease, 1.23 (1.04 to 1.45) and 1.85 (1.27 to 2.69) for coronary heart disease, and 1.15 (0.92 to 1.43) and 1.63 (1.14 to 2.34) for stroke. Relative risks for cadmium and copper were 1.33 (1.09 to 1.64) and 1.81 (1.05 to 3.11) for cardiovascular disease, 1.29 (0.98 to 1.71) and 2.22 (1.31 to 3.74) for coronary heart disease, and 1.72 (1.29 to 2.28) and 1.29 (0.77 to 2.17) for stroke. Mercury had no distinctive association with cardiovascular outcomes. There was a linear dose-response relation for arsenic, lead, and cadmium with cardiovascular disease outcomes.
CONCLUSION: Exposure to arsenic, lead, cadmium, and copper is associated with an increased risk of cardiovascular disease and coronary heart disease. Mercury is not associated with cardiovascular risk. These findings reinforce the importance of environmental toxic metals in cardiovascular risk, beyond the roles of conventional behavioural risk factors.

PMCID: PMC6113772
PMID: 30158148

Cardiol Rev. 2018 Aug 20.

## Hearts and Minds: Stress, Anxiety, and Depression. Unsung Risk Factors for Cardiovascular Disease.

Silverman AL, Herzog AA, Silverman DI.

Anxiety, depression and stress are exceedingly common in patients with cardiovascular disease (CVD). They increase the risk of cardiac events and are associated with much worse outcomes. A causal relationships exists between anxiety/depression and adverse cardiac events such as acute myocardial infarction and sudden cardiac death. Various treatments, including psychological therapies and pharmacotherapy, can used to treat patients with these disorders. This review discusses the epidemiology, pathogenesis and treatment options for patients with CVD who suffer from these conditions, and argues that they should be treated as concomitant risk factors for CVD.

PMID: 30130257

BioData Min. 2018 Aug 14;11:18.

## Evolutionary methods for variable selection in the epidemiological modeling of cardiovascular diseases.

Brester C, Kauhanen J, Tuomainen TP, Voutilainen S, Rönkkö M, Ronkainen K, Semenkin E, Kolehmainen M.

Background: The redundancy of information is becoming a critical issue for epidemiologists. High-dimensional datasets require new effective variable selection methods to be developed. This study implements an advanced evolutionary variable selection method which is applied for cardiovascular predictive modeling. The epidemiological follow-up study KIHD (Kuopio Ischemic Heart Disease Risk Factor Study) was used to compare the designed variable selection method based on an evolutionary search with conventional stepwise selection. The sample contains in total 433 predictor variables and a response variable indicating incidents of cardiovascular diseases for 1465 study subjects.

Results: The effectiveness of variable selection methods was investigated in combination with two models: Generalized Linear Logistic Regression and Support Vector Machine. We managed to decrease the number of variables from 433 to 38 and save the predictive ability of the models used. Their performance was evaluated with an F-score metric. At most, we gained 65.6% and 67.4% of the F-score before and after variable selection respectively. All the results were averaged over 5-folds of a cross-validation procedure.

Conclusions: The presented evolutionary variable selection method allows a reduced set of variables to be chosen which are relevant to predicting cardiovascular diseases. A reference list of the most meaningful variables is introduced to be used as a basis for new epidemiological studies. In general, the multicollinearity of variables enables different combinations of predictors to be used and the same performance of models to be attained.

PMCID: PMC6092817
PMID: 30127856

Eur Heart J. 2018 Aug 14.

## Epidemiology report: trends in sex-specific cerebrovascular disease mortality in Europe based on WHO mortality data.

Shah R, Wilkins E, Nichols M, Kelly P, El-Sadi F, Wright FL, Townsend N.

Aims: There have been substantial declines in cerebrovascular disease mortality across much of Europe, mirroring trends in deaths from cardiovascular disease as a whole. No study has investigated trends in cerebrovascular disease, and its subtypes within all European countries. This study aimed to examine sex-specific trends in cerebrovascular disease, and three of its sub-types: ischaemic stroke, haemorrhagic stroke, and subarachnoid haemorrhage (SAH), in Europe between 1980 and 2016.

Methods and results: Sex-specific mortality data for each country of the World Health Organization (WHO) Europe region were extracted from the WHO global mortality database and analysed using Joinpoint software to examine trends. The number and location of significant joinpoints for each country by sex and subtype was determined using a log-linear model. The annual percentage change within each segment was calculated along with the average annual percentage change over the duration of all available data. The last 35 years have seen large overall declines in cerebrovascular disease mortality rates in the majority of European countries. While these declines have continued steadily in more than half of countries, this analysis has revealed evidence of recent plateauing and even increases in stroke mortality in a number of countries, in both sexes, and in all four geographical sub-regions of Europe. Analysis by stroke sub-type revealed that recent plateauing was most common for haemorraghic stroke and increases were most common for ischaemic stroke.

Conclusion: These findings highlight the need for continued research into the inequalities in both current stroke mortality outcomes and trends across Europe, as well as the causes behind any recent plateauing of total cerebrovascular disease or its subtypes.

PMID: 30124820

Headache. 2018 Sep;58(8):1277-1286.

## Migraine and cerebrovascular diseases: Epidemiology, pathophysiological , and clinical considerations.

Magalhães JE, Sampaio Rocha-Filho PA.

Migraine and cerebrovascular diseases are disabling disorders, which are possibly closely interrelated. Heterogeneous and scattered evidence in literature remains a challenge. We searched for systematic reviews including diverse cerebrovascular events in migraineurs and reported relevant original studies to update the evidence when necessary. The studies show that migraine is associated with increased risk of transient ischemic attacks, any stroke, and possibly hemorrhagic stroke. In addition, migraine with aura increases the risk of ischemic stroke and white matter abnormalities. Migraine without aura increases the risk of cervical artery dissection as a cause of ischemic stroke. Groups with specific risk profiles are women, young people, smokers, and oral contraceptive users. The pathophysiology of the association remains uncertain. However, genetic and environmental factors may be involved in intricate mechanisms responsible for oxidative stress, vascular dysfunction and, ultimately, vascular events. In conclusion, migraine is a potential risk factor for cerebrovascular diseases. Migraineurs should be carefully evaluated considering their vascular risk assessment based on current evidence, so that healthcare professionals can provide appropriate and individualized management of other cardiovascular risk factors, notably quitting smoking and restricting use of oral contraceptives.

PMID: 30117565

J Am Coll Cardiol. 2018 Aug 21;72(8):914-926.

## Cardiovascular Disease Prevention by Diet Modification: JACC Health Promotion Series.

Yu E, Malik VS, Hu FB.

Reduction in excess calories and improvement in dietary composition may prevent many primary and secondary cardiovascular events. Current guidelines recommend diets high in fruits, vegetables, whole grains, nuts, and legumes; moderate in low-fat dairy and seafood; and low in processed meats, sugar-sweetened beverages, refined grains, and sodium. Supplementation can be useful for some people but cannot replace a good diet. Factors that influence individuals to consume a low-quality diet are myriad and include lack of knowledge, lack of availability, high cost, time scarcity, social and cultural norms, marketing of poor-quality foods, and palatability. Governments should focus on cardiovascular disease as a global threat and enact policies that will reach all levels of society and create a food environment wherein healthy foods are accessible, affordable, and desirable. Health professionals should be proficient in basic nutritional knowledge to promote a sustainable pattern of healthful eating for cardiovascular disease prevention for both healthy individuals and those at higher risk.

PMCID: PMC6100800 [Available on 2019-08-21]
PMID: 30115231

BMJ Open. 2018 Aug 1;8(7):e021704.

## Prevalence of atrial fibrillation and cardiovascular risk factors in a 63-65 years old general population cohort: the Akershus Cardiac Examination (ACE) 1950 Study.

Berge T, Lyngbakken MN, Ihle-Hansen H, Brynildsen J, Pervez MO, Aagaard EN, Vigen T, Kvisvik B, Christophersen IE, Steine K, Omland T, Smith P, Røsjø H, Tveit A.

OBJECTIVES: To investigate the sex-specific prevalence of atrial fibrillation (AF), including subclinical AF found by screening in a general population aged 63-65 years. The prevalence of cardiovascular risk factors and their association with AF will also be investigated. DESIGN: Cross-sectional analysis of an observational, prospective, longitudinal, population-based cohort study. SETTING: General population in Akershus county, Norway.
PARTICIPANTS: Women and men born in 1950. We included 3706 of 5827 eligible individuals (63.6%); 48.8% were women. METHODS: All participants underwent extensive cardiovascular examinations, including 12-lead ECG. History of AF and other cardiovascular diseases were self-reported. Subsequent validation of all reported or detected AF diagnoses was performed.
RESULTS: Mean age was 63.9±0.7 years. Prevalence of ECG-verified AF was 4.5% (women 2.4%, men 6.4%; p<0.001), including screen-detected AF in 0.3% (women 0.1%, men 0.6%; p<0.01). Hypertension was found in 62.0% (women 57.8%, men 66.0%; p<0.001). Overweight or obesity was found in 67.6% (women 59.8%, men 74.9%; p<0.001). By multivariate logistic regression, risk factors associated with AF were height (OR 1.67 per 10 cm; 95% CI 1.26 to 2.22; p<0.001), weight (OR 1.15 per 10 kg; 95% CI 1.01 to 1.30; p=0.03), hypertension (OR 2.49; 95% CI 1.61 to 3.86; p<0.001), heart failure (OR 3.51; 95% CI 1.71 to 7.24; p=0.001), reduced estimated glomerular filtration rate (OR 2.56; 95% CI 1.42 to 4.60; p<0.01) and at least one first-degree relative with AF (OR 2.32; 95% CI 1.63 to 3.31; p<0.001), whereas male sex was not significantly associated (OR 1.00; 95% CI 0.59 to 1.68; p=0.99).
CONCLUSION: In this cohort from the general population aged 63-65 years, we found a higher prevalence of known AF than previously reported below the age of 65 years. The additional yield of single time point screening for AF was low. Body size and comorbidity may explain most of the sex difference in AF prevalence at this age. TRIAL REGISTRATION NUMBER: NCT01555411; Results.

PMCID: PMC6074624 ; PMID: 30068617

Eur J Prev Cardiol. 2018 Sep;25(13):1387-1396.

## Loneliness, social isolation and risk of cardiovascular disease in the English Longitudinal Study of Ageing.

Valtorta NK, Kanaan M, Gilbody S, Hanratty B.

Background: There is increasing evidence of an association between social relationships and morbidity in general, and cardiovascular disease in particular. However, recent syntheses of the evidence raise two important questions: is it the perceived quality or the more objective quantity of relationships that matters most; and what are the implications of changes in relationships over time? In this study, we investigate the cumulative effects of loneliness and social isolation on incident cardiovascular disease.
Design: A secondary analysis of prospective follow-up data from the English Longitudinal Study of Ageing (ELSA). Methods To assess the association between social isolation or loneliness and incident cardiovascular disease, lagged values of exposure to loneliness and isolation were treated as time-varying variables in discrete time survival models controlling for potential confounders and established cardiovascular disease risk factors.
Results: A total of 5397 men and women aged over 50 years were followed up for new fatal and non-fatal diagnoses of heart disease and stroke between 2004 and 2010. Over a mean follow-up period of 5.4 years, 571 new cardiovascular events were recorded. We found that loneliness was associated with an increased risk of cardiovascular disease (odds ratio 1.27, 95% confidence interval 1.01-1.57). Social isolation, meanwhile, was not associated with disease incidence. There was no evidence of a cumulative effect over time of social relationships on cardiovascular disease risk.
Conclusions: Loneliness is associated with an increased risk of developing coronary heart disease and stroke, independently of traditional cardiovascular disease risk factors. Our findings suggest that primary prevention strategies targeting loneliness could help to prevent cardiovascular disease.

PMID: 30068233

J Am Heart Assoc. 2018 Jul 12;7(14). pii: e008078.

## Dietary Patterns and Mediterranean Diet Score and Hazard of Recurrent Coronary Heart Disease Events and All-Cause Mortality in the REGARDS Study.

Shikany JM, Safford MM, Bryan J, Newby PK, Richman JS, Durant RW, Brown TM, Judd SE.

BACKGROUND: Previously, we reported on associations between dietary patterns and incident acute coronary heart disease (CHD) in the REGARDS (Reasons for Geographic and Racial Differences in Stroke) study. Here, we investigated the associations of dietary patterns and a dietary index with recurrent CHD events and all-cause mortality in REGARDS participants with existing CHD.
METHODS AND RESULTS: We included data from 3562 participants with existing CHD in REGARDS. We used Cox proportional hazards regression to examine the hazard of first recurrence of CHD events-definite or probable MI or acute CHD death-and all-cause mortality associated with quartiles of empirically derived dietary patterns (convenience, plant-based, sweets, Southern, and alcohol and salads) and the Mediterranean diet score. Over a median 7.1 years (interquartile range, 4.4, 8.9 years) follow-up, there were 581 recurrent CHD events and 1098 deaths. In multivariable-adjusted models, the Mediterranean diet score was inversely associated with the hazard of recurrent CHD events (hazard ratio for highest score versus lowest score, 0.78; 95% confidence interval, 0.62-0.98; PTrend=0.036). The Southern dietary pattern was adversely associated with the hazard of all-cause mortality (hazard ratio for Q4 versus Q1, 1.57; 95% confidence interval, 1.28-1.91; PTrend<0.001). The Mediterranean diet score was inversely associated with the hazard of all-cause mortality (hazard ratio for highest score versus lowest score, 0.80; 95% confidence interval, 0.67-0.95; PTrend=0.014).
CONCLUSIONS: The Southern dietary pattern was associated with a greater hazard of all-cause mortality in REGARDS participants. Greater adherence to the Mediterranean diet was associated with both a lower hazard of recurrent CHD events and all-cause mortality.

PMCID: PMC6064845
PMID: 30005552

Am J Cardiol. 2018 Aug 15;122(4):571-577.

## Relation of Subclinical Hypothyroidism is Associated With Cardiovascular Events and All-Cause Mortality in Adults With High Cardiovascular Risk.

Moon S, Kong SH, Choi HS, Hwangbo Y, Lee MK, Moon JH, Jang HC, Cho NH, Park YJ.

The aim of this study was to determine the association between subclinical hypothyroidism and cardiovascular (CVD) events, and mortality using the atherosclerotic CVD risk score. We carried out an observational study in a prospective cohort that was followed up for 12 years. The study included 3,021 participants aged ≥ 40 years at baseline from the Ansung cohort, part of the Korean Genome and Epidemiology Study. Cox regression models were constructed to evaluate the hazards ratio (HR) and 95% confidence interval (CI) for all-cause mortality and CVD events in groups classified according to thyroid status. Subgroup analysis was performed with a cut-off age of 65 years or 7.5% of the 10-year atherosclerotic CVD risk score. The subclinical hypothyroidism group in the highest quartile of thyroid-stimulating hormone (>6.57 mIU/L) had a significantly increased risk of all-cause mortality (HR 2.12, 95% CI 1.27 to 3.56) and CVD events (HR 1.92, 95% CI 1.21 to 3.04) compared with euthyroid participants. Subgroup analysis by CVD risk revealed that participants with high CVD risk only had a high risk of all-cause mortality (HR 2.18, 95% CI 1.22 to 3.87) and CVD events (HR 2.42, 95% CI 1.35 to 4.33). Further analysis showed that participants aged <65 years with high CVD risk had the highest risk of all-cause mortality (HR 3.50, 95% CI 1.50 to 8.16) and CVD events (HR 3.37, 95% CI 1.46 to 9.57). Our results demonstrated that high thyroid-stimulating hormone levels were associated with a greater risk of mortality and new CVD risks, particularly among subjects with high CVD risk.

PMID: 29980273

Monaldi Arch Chest Dis. 2018 Jul 2;88(2):966.

## Best practice in psychological activities in cardiovascular prevention and rehabilitation: Position Paper.

Sommaruga M, Angelino E, Della Porta P, Abatello M, Baiardo G, Balestroni G, Bettinardi O, Callus E, Ciracì C, Omodeo O, Rizza C, Michielin P, Ambrosetti M, Griffo R, Pedretti RFE, Pierobon A.

Recent guidelines on cardiovascular disease prevention suggest multimodal behavioral interventions for psychosocial risk factors and referral for psychotherapy in the case of clinically significant symptoms of depression and anxiety overall. Accordingly, psychologists of the Italian Association for Cardiovascular Prevention, Rehabilitation and Epidemiology (GICR-IACPR) have reviewed the key components of psychological activities in cardiovascular prevention and rehabilitation (CPR). The aim of this study was to elaborate a position paper on the best practice in routine psychological activities in CPR based on efficacy, effectiveness and sustainability. The steps followed were: i) a review of the latest international guidelines and position papers; ii) analysis of the evidence-based literature; iii) a qualitative analysis of the psychological services operating in some reference Italian cardiac rehabilitation facilities; iv) classification of the psychological activities in CPR as low or high intensity based on the NICE Guidelines on psychological interventions on anxiety and depression. We confirm the existence of an association between depression, anxiety, social factors, stress, personality and illness onset/outcome and coronary heart disease. Evidence for an association between depression, social factors and disease outcome emerges particularly for chronic heart failure. Some positive psychological variables (e.g., optimism) are associated to illness outcome. Evidence is reported on the impact of psychological activities on 'new' conditions which are now indicated for cardiac rehabilitation: pulmonary hypertension, grown-up congenital heart, end-stage heart failure, implantable cardioverter-defribrillator and mechanical ventricular assist devices, frail and oldest-old patients, and end-of-life care. We also report evidence related to caregivers. The Panel divided evidence-based psychological interventions into: i) low intensity (counseling, psycho-education, self-care, self-management, telemedicine, self-help); or ii) high intensity (individual, couples and/or family and group psychotherapy, such as stress management). The results show that psychotherapy is mainly consisting of cognitive-behavior therapy, interpersonal therapy, and short-term psycho-dynamic therapy. The current data further refine the working tools available for psychological activities in CPR, giving clear directions about the choice of interventions, which should be evidence-based and have at least a

minimum standard. This document provides a comprehensive update on new knowledge and new paths for psychologists working in the CPR settings.

PMID: 29962189

High Blood Press Cardiovasc Prev. 2018 Sep;25(3):295-301

## Prevalence and Comorbidities of Resistant Hypertension: A Collaborative Population-Based Observational Study.

Romano S, Idolazzi C, Fava C, Fondrieschi L, Celebrano M, Delva P, Branz L, Donato A, Dalbeni A, Minuz P.

BACKGROUND: Resistant hypertension, is a clinical condition that may confer high cardiovascular risk. Aim of the observational study was to evaluate the prevalence of resistant hypertension, and the association with cardiovascular risk factors or diseases in the Verona urban area.
DESIGN AND METHODS: Eleven family doctors retrieved anonymised data concerning blood pressure, diagnosis of hypertension and treatments from a population of 17,502 adult subjects. The prevalence of resistant hypertension was estimated considering patients who had been consecutively treated with at least four antihypertensive medications, regardless of blood pressure values. Further search concerning the clinical characteristics associated with resistant hypertension was performed in a random subsample of 55 patients.
RESULTS: The prevalence of hypertension was 21.9%, that of resistant hypertension was 2.1%, approximately 10% of the whole hypertensive population. High prevalence of diabetes mellitus (53%) and hyperlipidemia (83%) was found in association with resistant hypertension. As for end organ damage, high prevalence of carotid artery stenosis (45%), ischemic heart disease (43%) and left ventricular hypertrophy (40%) was observed in patients with resistant hypertension. Blood pressure was higher than 140/90 mmHg in 58% of patients in spite of treatment with four or more different antihypertensive drugs. The average age, systolic and pulse pressure were significantly higher in the subgroup of patients with resistant hypertension.
CONCLUSIONS: Patients with resistant hypertension are characterised by a higher systolic and pulse pressure and a very high attributable cardiovascular risk, due to high prevalence of cardiovascular risk factors and overt organ damage and cardiovascular disease.

PMID: 29959696

Int Angiol. 2018 Aug;37(4):327-334.

## Epidemiology of peripheral artery disease in Europe: VAS Educational Paper.

Olinic DM, Spinu M, Olinic M, Homorodean C, Tataru DA, Liew A, Schernthaner GH, Stanek A, Fowkes G, Catalano M.

This paper reviews the current epidemiological data on peripheral artery disease (PAD) in Europe. Cardiovascular disease (CVD) burden is presented and PAD prevalence is discussed, as compared to coronary (CAD) and cerebrovascular (CeVD) diseases, in European Union (EU) countries and European continent countries. The article reviews PAD clinical manifestations, PAD diagnosis, risk factors for PAD incidence and progression, PAD prognosis and financial implications. CVD mortality is higher in women than in men and in European continent countries, as compared to EU countries. While CAD and CeVD have a lower prevalence in EU countries, as compared to the whole continent, PAD and other CVDs still have a higher prevalence in EU countries. PAD prevalence vary widely between countries, increases sharply with aging and has a relation with ethnicity. CVD comorbidities are high in PAD subjects and particularly high in those with critical limb ischemia. PAD prognosis is related to CAD and CeVD mortality, that are particularly high in critical limb ischemia. This review promotes the need for global awareness on PAD burden, stimulates PAD screening and emphasizes the importance of early diagnosis and treatment of PAD and associated cardiovascular comorbidities.

PMID: 29936722 [Indexed for MEDLINE]

Antioxid Redox Signal. 2018 Jul 25.

## Urinary Excretion of Sulfur Metabolites and Risk of Cardiovascular Events and All-Cause Mortality in the General Population.

van den Born JC, Frenay AS, Koning AM, Bachtler M, Riphagen IJ, Minovíc I, Feelisch M, Dekker MM, Bulthuis MLC, Gansevoort RT, Hillebrands JL, Pasch A, Bakker SJL, van Goor H.

AIMS: Thiosulfate and sulfate are metabolites of hydrogen sulfide (H2S), a gaseous signaling molecule with cardiovascular (CV) protective properties. Urinary thiosulfate excretion and sulfate excretion are associated with favorable disease outcome in high-risk patient groups. We investigated the relationship between urinary excretion of sulfur metabolites, and risk of CV events and all-cause mortality in the general population.
RESULTS: Subjects (n = 6839) of the Prevention of Renal and Vascular End-stage Disease (PREVEND) study were followed prospectively. At baseline, 24-h urinary excretion of thiosulfate and sulfate was determined. Median urinary thiosulfate and sulfate excretion values were 1.27 (interquartile range [IQR] 0.89-2.37) μmol/24 h and 15.7 (IQR 12.0-20.3) mmol/24 h, respectively. Neither thiosulfate nor sulfate excretion showed an independent association with risk of CV events. Sulfate, but not thiosulfate, was inversely associated with risk of all-cause mortality, independent of potential confounders (hazard ratio 0.73 [95% confidence interval 0.63-0.84], $p < 0.001$). This association appeared most pronounced for normolipidemic subjects ($p_{interaction} = 0.019$).
INNOVATION: The strong association between sulfate excretion and mortality in the general population emphasizes the (patho)physiological importance of sulfate or its precursor H2S.
CONCLUSION: We hypothesize that urinary sulfate excretion, which is inversely associated with all-cause mortality in the general population, holds clinical relevance as a beneficial modulator in health and disease. Antioxid. Redox Signal. 00, 000-000.

PMID: 29905081

Physiol Genomics. 2018 Sep 1;50(9):724-725.

## GNAI2 polymorphic variance associates with salt sensitivity of blood pressure in the Genetic Epidemiology Network of Salt Sensitivity study.

Zhang X, Frame AA, Williams JS, Wainford RD.

Salt sensitivity of blood pressure (BP) increases hypertension risk and associated adverse cardiovascular outcomes. At present, there are no validated rapid tests or diagnostic markers to identify salt sensitivity of BP in clinical practice. Based on our prior animal studies that report a role for brain Gαi2 proteins in the salt sensitivity of BP and evidence that GNAI2 single nucleotide polymorphisms (SNPs) associate with hypertension risk, we investigated the hypothesis that GNAI2 SNPs associate with salt sensitivity of BP in humans. Our data provide the first evidence that a GNAI2 SNP ( rs10510755 ) positively associates with salt sensitivity of BP in the Genetic Epidemiology of Salt Sensitivity data set (continuous phenotype P = 0.049, case-control phenotype P = 0.039; n = 968), independently of subject sex or age. These observations suggest that genotyping at GNAI2 may be a useful biomarker in identifying individuals at risk for developing salt-sensitive BP and related complications or in identifying salt sensitivity within the hypertensive population.

PMCID: PMC6172609
PMID: 29906209

Clin Chim Acta. 2018 Sep;484:150-163.

## Uric acid and cardiovascular disease.

Ndrepepa G.

Uric acid (UA) is an end product of purine metabolism in humans and great apes. UA acts as an antioxidant and it accounts for 50% of the total antioxidant capacity of biological fluids in humans. When present in cytoplasm of the cells or in acidic/hydrophobic milieu in atherosclerotic plaques, UA converts into a pro-oxidant agent and promotes oxidative stress and through this mechanism participates in the pathophysiology of human disease including cardiovascular disease (CVD). Most epidemiological studies but not all of them suggested the existence of an association between elevated serum UA level and CVD, including coronary heart disease (CHD), stroke, congestive heart failure, arterial hypertension and atrial fibrillation as well as an increased risk for mortality due to CVD in general population and subjects with confirmed CHD. Evidence available also suggests an association between elevated UA and traditional cardiovascular risk factors, metabolic syndrome, insulin resistance, obesity, non-alcoholic fatty liver disease and chronic kidney disease. Experimental and clinical studies have evidenced several mechanisms through which elevated UA level exerts deleterious effects on cardiovascular health including increased oxidative stress, reduced availability of nitric oxide and endothelial dysfunction, promotion of local and systemic inflammation, vasoconstriction and proliferation of vascular smooth muscle cells, insulin resistance and metabolic dysregulation. Although the causality in the relationship between UA and CVD remains unproven, UA may be pathogenic and participate in the pathophysiology of CVD by serving as a bridging mechanism mediating (enabling) or potentiating the deleterious effects of cardiovascular risk factors on vascular tissue and myocardium.

PMID: 29803897

Eur J Intern Med. 2018 Sep;55:28-34.

## Increased burden of comorbidities and risk of cardiovascular death in atrial fibrillation patients in Europe over ten years: A comparison between EORP-AF pilot and EHS-AF registries.

Proietti M, Laroche C, Nieuwlaat R, Crijns HJGM, Maggioni AP, Lane DA, Boriani G, Lip GYH; EORP-AF General Pilot Registry; Euro Heart Survey on AF Investigators.

BACKGROUND: In 2002, the European Society of Cardiology conducted the Euro Heart Survey (EHS), while in 2014concluded 1-year follow-up of the EURObservational Research Programme AF (EORP-AF) Pilot Registry.
METHODS: We analysed differences in clinical profiles, therapeutic approaches and outcomes between these two cohorts after propensity score matching (PSM).
RESULTS: After PSM, 5206 patients were analysed. In EORP-AF there were more elderly patients than EHS ($p < .001$). EORP-AF patients were more burdened with cardiovascular (CV) and non-CV comorbidities, with a higher proportion of patients with high thromboembolic risk. EORP-AF patients used more oral-anticoagulant (OAC) ($p < .001$). At 1-year follow-up EORP-AF patients had lower risk for thromboembolic and CV events, readmission for AF and other CV reasons (all $p < .001$), showing conversely a higher risk for CV death ($p = .015$). Kaplan-Meier curves showed that EORP-AF patients had higher risk for CV death ($p < .0001$) and all-cause death ($p = .0019$). Cox regression confirmed that
EORP-AF patients were at higher risk for CV death ($p = .021$).
CONCLUSIONS: We found significant changes in AF epidemiology over a decade in Europe, with older patients, more burdened with comorbidities. A greater use of OAC was found. Despite a reduction in risk for thromboembolic events, a high risk of CV-related death was still evident.

PMID: 29778588

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J Lipid Res. 2018 Jul;59(7):1266-1275.

## Hypertriglyceridemia and cardiovascular risk: a cautionary note about metabolic confounding.

Sniderman AD, Couture P, Martin SS, DeGraaf J, Lawler PR, Cromwell WC, Wilkins JT, Thanassoulis G.

Triglycerides are the conventional tool to measure VLDLs, whereas LDL cholesterol (LDL-C) is the conventional tool to measure LDLs. Multiple epidemiological studies, including a series of genetically based analyses, have demonstrated that cardiovascular risk is related to triglycerides independently of LDL-C, and this has led to a series of new therapeutic agents designed specifically to reduce plasma triglycerides. The triglyceride hypothesis posits that increased levels of triglycerides increase cardiovascular risk and decreasing plasma triglycerides decreases cardiovascular risk. In this work, we will examine the validity of the triglyceride hypothesis by detailing the biological complexities associated with hypertriglyceridemia, the genetic epidemiological evidence in favor of hypertriglyceridemia, the evidence from the fibrate randomized clinical trials relating triglycerides and clinical outcomes, and the completeness of the evidence from the initial studies of novel mutations and the therapeutic agents based on these mutations that lower triglycerides. Because of the multiple metabolic links between VLDL and LDL, we will try to demonstrate that measuring triglycerides and LDL-C alone are inadequate to document the lipoprotein profile. We will try to demonstrate that apoB must be measured, as well as triglycerides and cholesterol, to have an accurate estimate of lipoprotein status.

PMCID: PMC6027915 [Available on 2019-07-01]
PMID: 29769239

Hypertens Res. 2018 Jul;41(7):475-482.

## Seasonal blood pressure variation: implications for cardiovascular risk stratification.

Modesti PA, Rapi S, Rogolino A, Tosi B, Galanti G.

Long-term blood pressure variations contribute to an increased risk of cardiovascular events during cold season, requiring personalized management of antihypertensive medications in a single patient, and can influence the results of clinical trials and epidemiological surveys in population studies. In addition to blood pressure values, which guide the stratification of cardiovascular risk, other cardiovascular risk factor levels also tend to be higher in the winter months and lower in the summer months. The resultant estimation of individual cardiovascular risk may thus vary depending on the season. At the patient level, only a low value in the winter should thus be considered a true measure of low cardiovascular risk, whereas low values measured in the summer do not indicate a low risk in the winter. Likewise, estimations of cardiovascular risk in population studies may vary according to the period of the year. Efforts should thus be directed at considering the potential influence of seasonal variations in establishing "normal" and "high-risk" assessment at both the patient and population levels, integrating such data into clinical practice.

PMID: 29760460

J Pediatr. 2018 Aug;199:85-91

# Relationships of Anxiety and Depression with Cardiovascular Health in Youth with Normal Weight to Severe Obesity.

Gross AC, Kaizer AM, Ryder JR, Fox CK, Rudser KD, Dengel DR, Kelly AS.

OBJECTIVE: To evaluate the relationships of depression and anxiety symptoms with cardiovascular disease (CVD) risk factors and measures of vascular health in youth.
STUDY DESIGN: Participants (n=202) were 8- to 18-year-olds from a cross-sectional study evaluating cardiovascular health across a wide range of body mass index values (normal weight to severe obesity). CVD risk measurement included blood pressure, fasting lipids, glucose, insulin, carotid artery
intima-media thickness, compliance and distensibility, brachial artery flow-mediated dilation, carotid-radial artery pulse wave velocity, body fat percentage, and a metabolic syndrome cluster score. Anxiety and depression symptoms were self-reported on the Screen for Child Anxiety Related Disorders and Center for Epidemiological Studies Depression Scale for Children. Two sets of adjustment variables were used in evaluation of differences between those with and without anxiety or depression symptomatology for the CVD risk factor and vascular outcomes. The first set included adjustment for Tanner stage, sex, and race; the second was additionally adjusted for percent body fat.
RESULTS: Anxiety was not significantly associated with CVD risk factors or vascular health in either model. Depression was associated with high-density lipoprotein cholesterol, triglycerides, and metabolic syndrome cluster score; these relationships were attenuated when accounting for percent body fat.
CONCLUSIONS: When accounting for body fat, we found no clear relationship of self-reported depression or anxiety symptoms with CVD risk factors or vascular health in youth.

PMCID: PMC6063783 [Available on 2019-08-01]
PMID: 29754863

Int J Cardiol. 2018 Jul 1;262:99-105.

## Cardiovascular risk goes up as your mood goes down: Interaction of depression and socioeconomic status in determination of cardiovascular risk in the CONSTANCES cohort.

Wiernik E, Meneton P, Empana JP, Siemiatycki J, Hoertel N, Vulser H, Nabi H, Limosin F, Czernichow S, Goldberg M, Ozguler A, Zins M, Lemogne C.

Comment in
Int J Cardiol. 2018 Jul 1;262:108-109.

BACKGROUND: Recent evidence suggests that the association of psychological variables with the risk of coronary heart disease (CHD) might depend upon socioeconomic status (SES). However, it is unclear whether the association between depressive symptoms and CHD risk might differ according to three SES indicators (education, occupational status and household monthly income).
METHODS: Among 34,836 working participants of the French CONSTANCES cohort (16,221 men, mean age [SD]: 44.0 [10.4] years) without history of cardiovascular disease, depressive symptoms were assessed with the Center of Epidemiologic Studies Depression scale (CES-D). The Framingham risk equation calibrated to the French population estimated the participant's 10-year risk of CHD. Associations between depressive symptoms and CHD risk were estimated using linear regression
models in SES strata.
RESULTS: The estimated 10-year risk of CHD was 16.9% in men and 1.8% in women. In men, the increased CHD risk in those with (versus without) depressive symptoms was more pronounced as occupational status decreased, being 0.65% (-0.57; 1.88), 1.58% (0.50; 2.66) and 3.19% (1.30; 5.07) higher in individuals of high, medium and low occupational status, respectively (p for interaction: 0.01). In contrast, effect modification by education or household income was less evident, despite similar trends. In women, no effect modification was found whatever the SES indicator.
CONCLUSIONS: Depressive symptoms and 10-year estimated CHD risk were more tightly linked in individuals of lower SES, at least in men. Occupational status was the SES indicator that displays the most obvious effect modification on this association.

PMID: 29706397

Clin Rheumatol. 2018 Sep;37(9):2331-2340.

## Prevalence of cardiovascular disease and major risk factors in patients with rheumatoid arthritis: a multinational cross-sectional study.

Pappas DA, Nyberg F, Kremer JM, Lampl K, Reed GW, Horne L, Ho M, Onofrei A, Malaviya AN, Rillo OL, Radominski SC, Gal J, Gibofsky A, Popkova TV, Laurindo L, Kerzberg EM, Zahora R, Pons-Estel BA, Curtis JR, Furst DE, Greenberg JD.

To compare the prevalence of cardiovascular disease (CVD) and major CVD risk factors among rheumatoid arthritis (RA) patients enrolled in a large US and multinational registry. We compared CVD and CVD risk factor prevalence from 11 countries enrolled in the CORRONA US and CORRONA International registries; patients from the 10 ex-US participating countries were grouped by region
(Eastern Europe, Latin America, and India). Unadjusted summary data were presented for demographics and disease characteristics; comparisons for prevalence of CVD risk factors and CVD were age/gender standardized to the age/gender distribution of the US enrolled patients. Overall, 25,987 patients were included in this analysis. Compared to patients from the ex-US regions, US participants had longer disease duration and lower disease activity, yet were more likely to receive a biologic agent. Additionally, CORRONA US participants had the highest body mass index (BMI). Enrolled patients in India had the lowest BMI, were more rarely smokers, and had a low prevalence of hyperlipidemia, hypertension, and prior CVD compared to the US and other ex-US regions. Participants from Eastern Europe had a higher prevalence of hypertension and hyperlipidemia and highest prevalence of all manifestations of CVD. Differences in the prevalence of both CVD and major CVD risk factors were observed across the four regions investigated. Observed differences may be influenced by variations in both non-modifiable/modifiable characteristics of patient populations, and may contribute to heterogeneity on the observed safety of investigational and approved therapies in studies involving RA patients from different origins.

PMID: 29696436

J Hypertens. 2018 Jul;36(7):1427-1440

# Obesity and cardiovascular risk: a call for action from the European Society of Hypertension Working Group of Obesity, Diabetes and the High-risk Patient and European Association for the Study of Obesity: part A: mechanisms of obesity induced hypertension, diabetes and dyslipidemia and practice guidelines for treatment.

Kotsis V, Jordan J, Micic D, Finer N, Leitner DR, Toplak H, Tokgozoglu L, Athyros V, Elisaf M, Filippatos TD, Redon J, Redon P, Antza C, Tsioufis K, Grassi G, Seravalle G, Coca A, Sierra C, Lurbe E, Stabouli S, Jelakovic B, Nilsson PM.

: Obesity is a key factor for cardiovascular diseases and complications. Obesity is associated with hypertension, dyslipidemia and type II diabetes, which are the major predictors of cardiovascular disease in the future. It predisposes for atrial fibrillation, heart failure, sudden cardiac death, renal disease and ischemic stroke that are the main causes of cardiovascular hospitalization and mortality. As obesity and the cardiovascular effects on the vessels and the heart start early in life, even from childhood, it is important for health policies to prevent obesity very early before the disease manifestation emerge. Key roles in the prevention are strategies to increase physical exercise, reduce body weight and to prevent or treat hypertension, lipids disorders and diabetes earlier and efficiently to prevent cardiovascular complications.Epidemiology and mechanisms of obesity-induced hypertension, diabetes and dyslipidemia will be reviewed and the role of lifestyle modification and treatment strategies in obesity will be updated and analyzed. The best treatment options for people with obesity, hypertension, diabetes and dyslipidemia will discussed.

PMID: 29634663

Circulation. 2018 Aug 7;138(6):578-589.

## Relationship of Familial Hypercholesterolemia and High Low-Density Lipoprotein Cholesterol to Ischemic Stroke.

Beheshti S, Madsen CM, Varbo A, Benn M, Nordestgaard BG.

BACKGROUND: Familial hypercholesterolemia (FH) is a condition with very high concentrations of low-density lipoprotein (LDL) cholesterol and high risk of ischemic heart disease including myocardial infarction. However, there is limited and contradictory information on whether FH and high LDL cholesterol per se confer high risk of ischemic stroke. We tested the hypotheses that individuals in the general population with FH and/or high LDL cholesterol have higher risk of ischemic stroke. METHODS: The associations of FH and high LDL cholesterol with ischemic stroke risk were tested in both causal, genetic, and observational analyses using 106412 individuals from the CGPS (Copenhagen General Population Study; 2823 ischemic strokes and 3792 myocardial infarctions) and/or 10 372 individuals from the CCHS (Copenhagen City Heart Study; 945 ischemic strokes and 1142 myocardial infarctions). FH causative mutations were LDLR W23X(rs267607213), W66G(rs121908025) and W556S, and APOB R3500Q(rs5742904). A Mendelian randomization design tested whether high LDL cholesterol per se has a causal effect on ischemic stroke risk, using a combination of the FH causative mutations and common genetic variants associated with high LDL cholesterol.
RESULTS: The cumulative incidences in individuals in the CGPS with and without FH causative mutations were similar for ischemic stroke ( P=0.50) but not for myocardial infarction ( P<0.001): at age 80 years, 4% and 7% of these individuals developed ischemic stroke and 20% and 8% myocardial infarction, with similar results in the CCHS. There was no association between clinical FH and ischemic stroke, except if personal premature ischemic heart disease was included in the clinical FH criteria. Ischemic heart disease at baseline was associated with higher ischemic stroke risk, explaining the higher ischemic stroke risk in those with high LDL cholesterol. For a 1 mmol/L higher LDL cholesterol, the genetic causal risk ratio was 1.11 (0.62-2.02) for ischemic stroke and 1.45 (1.08-1.93) for myocardial infarction.
CONCLUSIONS: FH and high LDL cholesterol did not confer an increased risk of ischemic stroke. A positive association with ischemic stroke observed for some clinical FH criteria and high LDL cholesterol appears to be due to previous ischemic heart disease, rather than to high LDL cholesterol per se.

PMID: 29593013

J Am Coll Nutr. 2018 Jul;37(5):429-455

## Functional Food and Cardiovascular Disease Prevention and Treatment: A Review.

Asgary S, Rastqar A, Keshvari M.

Cardiovascular disease (CVD) is now the leading cause of death globally and is a growing health concern. Lifestyle factors, including nutrition, play an important role in the etiology and treatment of CVD. Functional foods based on their basic nutritional functions can decrease the risk of many chronic diseases and have some physiological benefits. They contain physiologically active components either from plant or animal sources, marketed with the claim of their ability to reduce heart disease risk, focusing primarily on established risk factors, which are hyperlipidemia, diabetes, metabolic syndrome, obesity/overweight, elevated lipoprotein A level, small dense low-density lipoprotein cholesterol (LDL-C), and elevated inflammatory marker levels. Functional foods are suspected to exert their cardioprotective effects mainly through blood lipid profile level and improve hypertension control, endothelial function, platelet aggregation, and antioxidant actions. Clinical and epidemiological observations indicate that vegetable and fruit fiber, nuts and seeds, sea foods, coffee, tea, and dark chocolate have cardioprotective potential in humans, as well whole-grain products containing intact grain kernels rich in fiber and trace nutrients. They are nutritionally more important because they contain phytoprotective substances that might work synergistically to reduce cardiovascular risk. This review will focus on the reciprocal interaction between functional foods and the potential link to cardiovascular health and the possible mechanisms of action.

PMID: 29528772

Am J Epidemiol. 2018 Jul 1;187(7):1520-1529.

## Hemoglobin A1c Level and Cardiovascular Disease Incidence in Persons With Type 1 Diabetes: An Application of Joint Modeling of Longitudinal and Time-to-Event Data in the Pittsburgh Epidemiology of Diabetes Complications Study.

Miller RG, Anderson SJ, Costacou T, Sekikawa A, Orchard TJ.

Type 1 diabetes (T1D) is associated with increased risk of cardiovascular disease (CVD), but hyperglycemia (measured by hemoglobin A1c (HbA1c) level), which characterizes T1D, has itself been an inconsistent predictor of CVD incidence. However, only baseline HbA1c or a summary measure (e.g., mean level over follow-up) is usually analyzed. Joint models allow simultaneous modeling of repeatedly measured longitudinal covariates, using random effects, and time-to-event data. We evaluated data from the Pittsburgh Epidemiology of Diabetes Complications Study, an ongoing prospective cohort study of childhood-onset T1D that has followed participants since 1986-1988 and has repeatedly found little association between baseline HbA1c or mean follow-up HbA1c and coronary artery disease incidence. Of 561 participants without CVD at baseline, 263 (46.9%) developed CVD over a period of 25 years (1986-2014). In joint models, each 1% unit increase in HbA1c trajectory was associated with a 1.26-fold increased risk of CVD (95% confidence interval: 1.07, 1.45), after adjustment for baseline levels of other CVD risk factors, and a 1.13-fold increased risk (95% confidence interval: 0.99, 1.32) after adjustment for updated mean levels of other CVD risk factors. These findings, which support the need for good glycemic control to prevent CVD in persons with T1D, underscore the importance of utilizing methods incorporating within-subject variation over time when analyzing and interpreting longitudinal cohort study data.

PMCID: PMC6030923 [Available on 2019-07-01]
PMID: 29394305

Heart. 2018 Sep 12. pii: heartjnl-2018-313439.

## Cardiovascular risk model performance in women with and without hypertensive disorders of pregnancy.

Dam V, Onland-Moret NC, Verschuren WMM, Boer JMA, Benschop L, Franx A, Moons KGM, Boersma E, van der Schouw YT; CREW-consortium.

OBJECTIVES: Compare the predictive performance of Framingham Risk Score (FRS), Pooled Cohort Equations (PCEs) and Systematic COronary Risk Evaluation (SCORE) model between women with and without a history of hypertensive disorders of pregnancy (hHDP) and determine the effects of recalibration and refitting on predictive performance.
METHODS: We included 29751 women, 6302 with hHDP and 17369 without. We assessed whether models accurately predicted observed 10-year cardiovascular disease (CVD) risk (calibration) and whether they accurately distinguished between women developing CVD during follow-up and not (discrimination), separately for women with and without hHDP. We also recalibrated (updating intercept and slope) and refitted (recalculating coefficients) the models.
RESULTS: Original FRS and PCEs overpredicted 10-year CVD risks, with expected: observed (E:O) ratios ranging from 1.51 (for FRS in women with hHDP) to 2.29 (for PCEs in women without hHDP), while E:O ratios were close to 1 for SCORE. Overprediction attenuated slightly after recalibration for FRS and PCEs in both hHDP groups. Discrimination was reasonable for all models, with C-statistics
ranging from 0.70-0.81 (women with hHDP) and 0.72-0.74 (women without hHDP). C-statistics improved slightly after refitting 0.71-0.83 (with hHDP) and 0.73-0.80 (without hHDP). The E:O ratio of the original PCE model was statistically significantly better in women with hHDP compared with women without hHDP.
CONCLUSIONS: SCORE performed best in terms of both calibration and discrimination, while FRS and PCEs overpredicted risk in women with and without hHDP, but improved after recalibrating and refitting the models. No separate model for women with hHDP seems necessary, despite their higher baseline risk.

PMID: 30209122

# *Outcomes* Cardiovasculares

Pesquisa Bibliográfica efectuada em Pubmed (www.ncbi.nlm.nih.gov/ - Jul a Set 2018

N Engl J Med. 2018 Nov 7. [Epub ahead of print]

## Alirocumab and Cardiovascular Outcomes after Acute Coronary Syndrome.

Schwartz GG, et al.; ODYSSEY OUTCOMES Committees and Investigators.

BACKGROUND: Patients who have had an acute coronary syndrome are at high risk for recurrent ischemic cardiovascular events. We sought to determine whether alirocumab, a human monoclonal antibody to proprotein convertase subtilisin-kexin type 9 (PCSK9), would improve cardiovascular outcomes after an acute coronary syndrome in patients receiving high-intensity statin therapy.

METHODS: We conducted a multicenter, randomized, double-blind, placebo-controlled trial involving 18,924 patients who had an acute coronary syndrome 1 to 12 months earlier, had a low-density lipoprotein (LDL) cholesterol level of at least 70 mg per deciliter (1.8 mmol per liter), a non-high-density lipoprotein cholesterol level of at least 100 mg per deciliter (2.6 mmol per liter), or an apolipoprotein B level of at least 80 mg per deciliter, and were receiving statin therapy at a high-intensity dose or at the maximum tolerated dose. Patients were randomly assigned to receive alirocumab subcutaneously at a dose of 75 mg (9462 patients) or matching placebo (9462 patients) every 2 weeks. The dose of alirocumab was adjusted under blinded conditions to target an LDL cholesterol level of 25 to 50 mg per deciliter (0.6 to 1.3 mmol per liter). The primary end point was a composite of death from coronary heart disease, nonfatal myocardial infarction, fatal or nonfatal ischemic stroke, or unstable angina requiring hospitalization.

RESULTS: The median duration of follow-up was 2.8 years. A composite primary end-point event occurred in 903 patients (9.5%) in the alirocumab group and in 1052 patients (11.1%) in the placebo group (hazard ratio, 0.85; 95% confidence interval [CI], 0.78 to 0.93; P<0.001). A total of 334 patients (3.5%) in the alirocumab group and 392 patients (4.1%) in the placebo group died (hazard ratio, 0.85; 95% CI, 0.73 to 0.98). The absolute benefit of alirocumab with respect to the composite primary end point was greater among patients who had a baseline LDL cholesterol level of 100 mg or more per deciliter than among patients who had a lower baseline level. The incidence of adverse events was similar in the two groups, with the exception of local injection-site reactions (3.8% in the alirocumab group vs. 2.1% in the placebo group).

CONCLUSIONS: Among patients who had a previous acute coronary syndrome and who were receiving high-intensity statin therapy, the risk of recurrent ischemic cardiovascular events was lower among those who received alirocumab than among those who received placebo. (Funded by Sanofi and Regeneron Pharmaceuticals; ODYSSEY OUTCOMES ClinicalTrials.gov number, NCT01663402 .). PMID: 30403574

Heart Vessels. 2018 Sep 10.

## Comparison of effects of aldosterone receptor antagonists spironolactone and eplerenone on cardiovascular outcomes and safety in patients with acute decompensated heart failure.

Yamamoto M, Seo Y, Ishizu T, Nishi I, Hamada-Harimura Y, Machino-Ohtsuka T, Higuchi H, Sai S, Nakatsukasa T, Sugano A, Baba M, Obara K, Aonuma K.

Differences in the clinical impacts of the aldosterone receptor antagonists spironolactone and eplerenone in patients with heart failure (HF) are unclear. Among 838 prospectively enrolled patients hospitalized for HF, 90 treated with eplerenone were compared with 90 treated with spironolactone. The primary endpoint was a composite of cardiovascular death and hospitalization. A serial evaluation of the clinical parameters was performed 1 year after discharge. The mean dose of spironolactone was 27 ± 8 mg and of eplerenone was 34 ± 15 mg. During follow-up (mean 594 ± 317 days), primary endpoints occurred in 27 patients in the eplerenone group (30.0%) and 25 patients in the spironolactone group (27.8%). There were no significant intergroup differences in the primary endpoint (log-rank, p = 0.956). Serial changes in left ventricular ejection fraction, serum brain natriuretic peptide, systolic blood pressure, and estimated glomerular filtration rate did not differ significantly between groups. Although gynecomastia in men was common in the spironolactone group (p = 0.018), the discontinuation rates due to adverse events were similar in the two groups (p = 0.135). Subgroup analyses suggested that eplerenone was associated with a lower hazard rate of the primary endpoint in female patients (interaction, p = 0.076). Among patients with HF, eplerenone and spironolactone have similar impacts on cardiovascular outcomes and safety.

PMID: 30203391

Atherosclerosis. 2018 Oct;277:108-112.

## Mean platelet volume and long-term cardiovascular outcomes in patients with stable coronary artery disease.

Wada H, Dohi T, Miyauchi K, Shitara J, Endo H, Doi S, Tsuboi S, Ogita M, Iwata H, Kasai T, Okazaki S, Isoda K, Suwa S, Daida H.

BACKGROUND AND AIMS: Although an elevated mean platelet volume (MPV) has been associated with poor clinical outcomes after acute coronary syndrome (ACS), the association between MPV and long-term outcomes in patients with stable coronary artery disease (CAD) remains uncertain. We aimed to investigate the impact of pre-procedural MPV levels in patients following elective percutaneous coronary intervention (PCI).
METHODS: We studied 2872 stable CAD patients who underwent their first PCI and who had available data on pre-procedural MPV between 2002 and 2016. Patients were divided into quartiles based on their MPV. The incidences of major adverse cardiac events (MACE), including all-cause death and non-fatal myocardial infarction, were evaluated.
RESULTS: The median MPV was 10.4 fL (interquartile range: 9.8-11.0). During a median follow-up of 5.6 years, 498 (17.3%) MACE were identified, with a cumulative incidence significantly higher in the lowest MPV group than in other groups ($p < 0.01$). After adjustment for platelet count and the other cardiovascular risk factors, the lowest MPV group had a significantly higher risk of MACE compared with the highest MPV groups (hazard ratio: 1.43, 95% confidence interval 1.10-1.86, $p = 0.009$). Decreasing MPV as a continuous variable was associated with the incidence of MACE (hazard ratio: 1.16 per 1 fL decrease, 95% confidence interval 1.04-1.30, $p = 0.007$).
CONCLUSIONS: Contrary to previous studies on ACS patients, this study showed that a low MPV was associated with worse clinical outcomes among stable CAD patients.

PMID: 30195145

J Card Fail. 2018 Sep 5. pii: S1071-9164(18)30950-3.

## One-Year Cardiovascular Outcomes in Patients With Peripartum Cardiomyopathy.

Dayoub EJ, Datwani H, Lewey J, Groeneveld PW.

BACKGROUND: Peripartum cardiomyopathy (PPCM) is an important cause of obstetrical morbidity. Few large national studies have investigated the cardiovascular outcomes of women with PPCM, particularly beyond the immediate postpartum period. We examined the cardiovascular outcomes of 1-year survivors of PPCM in a large commercially insured population.

METHODS AND RESULTS: A retrospective cohort study was conducted with the use of administrative claims from patients aged 15-54years insured by a national commercial payer during 2005-2012. Women with PPCM were identified and matched by means of propensity score modeling to a control cohort of women undergoing childbirth without cardiovascular complications by demographics, comorbidities, and delivery year. Incidence of cardiovascular complications was measured from 11 to 365days after delivery. A total of 975 women with PPCM were included in the study. At 1 year after delivery, the most common major adverse cardiovascular events (MACEs) among the PPCM group were venous thromboembolism (2.2% vs 0.4%; P = .001), subsequent heart failure hospitalization (1.6% vs 0.1%; P < .001), and atrial fibrillation (1.0% vs 0%; P = .008). The PPCM cohort had a greater incidence of MACEs compared with matched control subjects (6.3% vs 0.6%; P < .001).

CONCLUSIONS: In PPCM survivors at 1 year, substantial morbidity continues to occur beyond the peripartum period, with venous thromboembolism and subsequent heart failure hospitalization being the most common complications.

PMID: 30194024

Sci Rep. 2018 Sep 3;8(1):13155. doi: 10.1038/s41598-018-31549-5.

## Blood Pressure Control and Cardiovascular Outcomes: Real-world Implications of the 2017 ACC/AHA Hypertension Guideline.

Lee JH, Kim SH, Kang SH, Cho JH, Cho Y, Oh IY, Yoon CH, Lee HY, Youn TJ, Chae IH, Kim CH.

The 2017 American College of Cardiology/American Heart Association (ACC/AHA) hypertension guideline lowered the threshold defining hypertension and treatment target from 140/90 mmHg to 130/80 mmHg. We compared the 2017 ACC/AHA guideline and the Eighth Joint National Committee (JNC8) report with regard to the current status of hypertension using the Korean National Health and Nutrition Examination Survey. The association between blood pressure (BP) control and long-term major cardiovascular outcomes (MACEs) was analyzed using the Korea National Health Insurance Service cohort. In the cross-sectional study with 15,784 adults, the prevalence of hypertension was expected to be 49.2±0.6% based on the definition suggested by the 2017 ACC/AHA guideline versus 30.4±0.6% based on the JNC8 report. In a longitudinal analysis with 373,800 hypertensive adults for the median follow-up periods of 11.0 years, the adults meeting the target goal BP goal of 2017 ACC/AHA guideline were associated with 21% reduced risk of MACEs compared with adults, not meeting 2017 ACC/AHA BP goal but meeting JNC8 target goal. In conclusion, substantial increase of prevalence of hypertension is expected by the 2017 ACC/AHA guideline. This study also suggests endorsing the aggressive approach would lead to an improvement in cardiovascular care.

PMCID: PMC6120944
PMID: 30177714

Nephrol Dial Transplant. 2018 Aug 28.

## The relationship between urinary albumin excretion, cardiovascular outcomes and total mortality among a large cohort of insulin-treated patients with type 2 diabetes in routine primary care practices.

Anyanwagu U, Donnelly R, Idris I.

Background: Albuminuria is a recognized diagnostic and prognostic marker of chronic kidney disease and cardiovascular (CV) risk but the well-known relationship between increments in urinary albumin:creatinine ratio (UACR) and CV outcomes and mortality has not been fully explored in insulin-treated patients with type 2 diabetes (T2D) in routine clinical care.
Methods: We investigated data for insulin users with T2D from UK general practices between 2007 and 2014. The UACR at the time of insulin initiation was measured and categorized as <10, 10- 29, 30-300 and >300 mg/g. Patients were followed up for 5 years or the earliest occurrence of all-cause mortality, non-fatal myocardial infarction or stroke. Cox proportional hazards models were fitted to estimate the risk of a composite of these events.
Results: A total of 12725 patients with T2D (mean age 58.6 ± 13.8 years, mean haemoglobin A1c 8.7 ± 1.8%) initiating insulin therapy between 2007 and 2014 met the inclusion criteria. Compared with patients whose ACR levels at insulin initiation were <10 mg/g, the adjusted risk of the 3-point composite endpoint was 9, 30 and 98% higher in those with ACR levels between 10-29, 30-300 and >300 mg/g, respectively, after a follow-up period of 5 years. The ACR category on its own did not predict risk of all-cause mortality.
Conclusions: This study shows that in patients with T2D on insulin therapy, increased urinary ACR is independently associated with an increased risk of major adverse CV events and all-cause mortality.

PMID: 30169825

Clin Res Cardiol. 2018 Aug 24.

## Influence of baseline systolic blood pressure on the relationship between intensive blood pressure control and cardiovascular outcomes in the Systolic Blood Pressure Intervention Trial (SPRINT).

Sun X, Guo Y, Nie Z, Cheng J, Zhou H, Zhong X, Zhang S, Du Z, Zhuang X, Liao X.

OBJECTIVE: To determine whether the effects of intensive (<120 mmHg) compared with standard (<140 mmHg) systolic blood pressure (SBP) treatments are different among those with different baseline SBP.
METHODS: De-identified SPRINT database was used for this post hoc analysis. SPRINT participants were categorized by baseline SBP status, defined as high-SBP (≥140 mmHg) group versus the low-SBP (<140 mmHg) group. The primary outcome was a composite of myocardial infarction, acute coronary syndrome not resulting in myocardial infarction, stroke, acute decompensated heart failure, or death from cardiovascular causes. Treatment-related adverse events including hypotension, syncope, and bradycardia were also evaluated. Cox regression was used to calculate hazard ratios for study outcomes with intensive compared with standard SBP treatment between these two groups.
RESULTS: Among 9361 participants randomized (age 67.9±9.4 years; 35.5% female), 4964 and 4397 had baseline low SBP (<140 mmHg) and high SBP (≥140 mmHg), respectively. After a median follow-up of 3.26 years, the hazard ratio for the primary outcome was 0.65 (95% CI 0.50, 0.83) and 0.84 (95% CI 0.66, 1.06) among those in the low-SBP group and high-SBP group, respectively (P value for interaction 0.15). For treatment-related adverse events, the hazard ratio with intensive SBP treatment was 2.03 (95% CI 1.44, 2.85) for the low-SBP group and 1.80 (95% CI 1.32, 2.47) for the high-SBP group (P value for interaction 0.28).
CONCLUSIONS: Hypertensive patients with low baseline SBP may benefit from intensive SBP lowering, whereas benefits were inconclusive among those with high baseline SBP.

PMID: 30167807

Curr Treat Options Cardiovasc Med. 2018 Aug 28;20(10):84.

## The "Extreme Exercise Hypothesis": Recent Findings and Cardiovascular Health Implications.

Eijsvogels TMH, Thompson PD, Franklin BA.

PURPOSE OF REVIEW: The "Extreme Exercise Hypothesis" is characterized by a U-shaped or reverse J-shaped, dose-response curve between physical activity volumes and cardiovascular health outcomes. In this review, we summarize recent findings that may support or refute the "Extreme Exercise Hypothesis." Furthermore, we discuss potential cardiovascular health implications of the cardiac anatomical, structural, contractility, and biomarker abnormalities that have been reported in some veteran endurance athletes.

RECENT FINDINGS: Emerging evidence from epidemiological studies and observations in cohorts of endurance athletes suggest that potentially adverse cardiovascular manifestations may occur following high-volume and/or high-intensity long-term exercise training, which may attenuate the health benefits of a physically active lifestyle. Accelerated coronary artery calcification, exercise-induced cardiac biomarker release, myocardial fibrosis, atrial fibrillation, and even higher risk of sudden cardiac death have been reported in athletes. There is primarily circumstantial evidence that supports the "Extreme Exercise Hypothesis." Subclinical and atherosclerotic coronary artery disease (CAD) as well as structural cardiovascular abnormalities and arrhythmias are present in some of the most active veteran endurance athletes and need appropriate clinical follow-up to reduce the risk for adverse cardiovascular outcomes. Future studies are warranted to establish the long-term cardiovascular health effects of these findings in veteran endurance athletes.

PMCID: PMC6132728
PMID: 30155804

Appl Physiol Nutr Metab. 2018 Aug 27.

## Very Low Load Resistance Exercise in the Upper Body with and without Blood Flow Restriction: Cardiovascular Outcomes.

Mouser JG, Mattocks KT, Dankel SJ, Buckner SL, Jessee MB, Bell ZW, Abe T, Loenneke JP.

It is proposed that, at very low loads, greater blood flow restriction (BFR) pressures might be required for muscular adaptation to occur. The cardiovascular and hyperemic response to very low loads combined with relative levels of BFR is unknown.
METHODS: Ninety-seven participants were recruited and assigned to one of four exercise conditions: 15% of one-repetition maximum (1RM) without BFR (15/00), 15% 1RM with BFR at 40% of arterial occlusion pressure (AOP) (15/40), 15% of 1RM with BFR at 80% of AOP (15/80), and 70% of 1RM without BFR (70/00). Participants performed four sets of unilateral biceps curls. Blood pressure was measured before/after exercise; brachial artery blood flow was measured before, following the 2nd set, and one minute following exercise.
RESULTS: Systolic blood pressure increased following exercise in all conditions (+10 (11) mmHg, $P < .0005$). Diastolic pressure increased in all but 70/00 (+2 (11) mmHg, $P = .107$). Brachial artery blood flow increased following the 2nd set of exercise in all but 15/80 (+43.4 (76.8) ml·min-1, $P = .348$). One minute following exercise and cuff deflation, there were no differences in blood flow between conditions ($P > .05$). Similarly, artery diameter was increased in all conditions except 15/80 (+0.002 (0.041) cm, $P = .853$) following the 2nd set, and increased in all conditions by one minute following exercise ($P < .05$).
CONCLUSION: Exercise-induced hyperemia is blunted with increasing pressures of BFR. There is a modest increase in blood pressure at very low loads of resistance exercise in the upper body.

PMID: 30148969

Open Med (Wars). 2018 Aug 21;13:304-323.

## Control of Blood Pressure and Cardiovascular Outcomes in Type 2 Diabetes.

Vargas-Uricoechea H, Cáceres-Acosta MF.

High blood pressure in patients with diabetes mellitus results in a significant increase in the risk of cardiovascular events and mortality. The current evidence regarding the impact of intervention on blood pressure levels (in accordance with a specific threshold) is not particularly robust. Blood pressure control is more difficult to achieve in patients with diabetes than in non-diabetic patients, and requires using combination therapy in most patients. Different management guidelines recommend initiating pharmacological therapy with values >140/90 mm/Hg; however, an optimal cut point for this population has not been established. Based on the available evidence, it appears that blood pressure targets will probably have to be lower than <140/90mmHg, and that values approaching 130/80mmHg should be recommended. Initial treatment of hypertension in diabetes should include drug classes demonstrated to reduce cardiovascular events; i.e., angiotensin converting-enzyme inhibitors, angiotensin receptor blockers, diuretics, or dihydropyridine calcium channel blockers. The start of therapy must be individualized in accordance with the patient's baseline characteristics, and factors such as associated comorbidities, race, and age, inter alia.

PMCID: PMC6104200
PMID: 30140748

J Clin Lipidol. 2018 Jul 25. pii: S1933-2874(18)30308-8.

## Cardiovascular outcomes during extended follow-up of the AIM-HIGH trial cohort.

Probstfield JL, Boden WE, Anderson T, Branch K, Kashyap M, Fleg JL, Desvigne-Nickens P, McBride R, McGovern M; AIM-HIGH Investigators.

BACKGROUND: Epidemiologic studies have shown that low levels of high-density lipoprotein-cholesterol (HDL-C) and elevated triglycerides are independent predictors of cardiovascular (CV) events, though randomized trials of HDL-C-raising therapies to reduce clinical events have been largely disappointing. The Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides and Impact on Global Health Outcomes (AIM-HIGH) trial failed to show that extended release niacin (ERN) reduced CV events in patients with atherogenic dyslipidemia who were on statin-based therapy.
OBJECTIVE: We sought to determine whether extended follow-up of AIM-HIGH participants changed these null results.
METHODS: AIM-HIGH was a placebo-controlled trial of 3414 patients with established CV disease, low baseline HDL-C, and elevated triglycerides levels randomized to ERN 1500-2000 mg/d vs placebo. Participants also received simvastatin with or without ezetimibe to attain on-treatment low-density lipoprotein cholesterol levels of 40-80 mg/dL. The trial was halted after a mean 3-year follow-up because of futility.
RESULTS: Among 3236 participants alive at the end of blinded study, 2613 (81%; ERN = 1,312, placebo = 1301) were followed a mean 1.1 additional years. Ninety-five percent of subjects remained on statin, but only 4% on ERN. At a mean total follow-up of 4.1 years, there were 343 primary CV endpoints in the ERN arm and 305 CV endpoints in placebo participants (HR 1.11, 95% CI 0.96, 1.30). Ischemic stroke was also not significantly different after extended follow-up in the two groups (2.2% vs 1.5%, P = .13).
CONCLUSIONS: In patients with CV disease and atherogenic dyslipidemia on statin-based therapy, 3 years of ERN treatment did not lower CV event rates. An additional year of follow-up off assigned treatment did not alter these findings.

PMID: 30131256

N Engl J Med. 2018 Aug 16;379(7):633-644.

## Risk Factors, Mortality, and Cardiovascular Outcomes in Patients with Type 2 Diabetes.

Rawshani A, Rawshani A, Franzén S, Sattar N, Eliasson B, Svensson AM, Zethelius B, Miftaraj M, McGuire DK, Rosengren A, Gudbjörnsdottir S.

Comment in N Engl J Med. 2018 Aug 16;379(7):684-685.

BACKGROUND: Patients with diabetes are at higher risk for death and cardiovascular outcomes than the general population. We investigated whether the excess risk of death and cardiovascular events among patients with type 2 diabetes could be reduced or eliminated. METHODS: In a cohort study, we included 271,174 patients with type 2 diabetes who were registered in the Swedish National Diabetes Register and matched them with 1,355,870 controls on the basis of age, sex, and county. We assessed patients with diabetes according to age categories and according to the presence of five risk factors (elevated glycated hemoglobin level, elevated low-density lipoprotein cholesterol level, albuminuria, smoking, and elevated blood pressure). Cox regression was used to study the excess risk of outcomes (death, acute myocardial infarction, stroke, and hospitalization for heart failure) associated with smoking and the number of variables outside target ranges. We also examined the relationship between various risk factors and cardiovascular outcomes. RESULTS: The median follow-up among all the study participants was 5.7 years, during which 175,345 deaths occurred. Among patients with type 2 diabetes, the excess risk of outcomes decreased stepwise for each risk-factor variable within the target range. Among patients with diabetes who had all five variables within target ranges, the hazard ratio for death from any cause, as compared with controls, was 1.06 (95% confidence interval [CI], 1.00 to 1.12), the hazard ratio for acute myocardial infarction was 0.84 (95% CI, 0.75 to 0.93), and the hazard ratio for stroke was 0.95 (95% CI, 0.84 to 1.07). The risk of hospitalization for heart failure was consistently higher among patients with diabetes than among controls (hazard ratio, 1.45; 95% CI, 1.34 to 1.57). In patients with type 2 diabetes, a glycated hemoglobin level outside the target range was the strongest predictor of stroke and acute myocardial infarction; smoking was the strongest predictor of death. CONCLUSIONS: Patients with type 2 diabetes who had five risk-factor variables within the target ranges appeared to have little or no excess risk of death, myocardial infarction, or stroke, as compared with the general population. (Funded by the Swedish Association of Local Authorities and Regions and others.).

PMID: 30110583 [Indexed for MEDLINE]

Am J Cardiol. 2018 Oct 1;122(7):1113-1120.

## Heart Rate as a Predictor of Outcome Following Percutaneous Coronary Intervention.

O'Brien J, Reid CM, Andrianopoulos N, Ajani AE, Clark DJ, Krum H, Loane P, Freeman M, Sebastian M, Brennan AL, Shaw J, Dart AM, Duffy SJ; Melbourne Interventional Group Investigators.

Data from previous studies of patients with heart failure and coronary artery disease suggest that those with higher resting heart rates (HRs) have worse cardiovascular outcomes. We sought to evaluate whether HR immediately before percutaneous coronary intervention (PCI) is an independent predictor for 30-day outcome. We analyzed the outcome of 3,720 patients who had HR recorded before PCI from the Melbourne Interventional Group registry. HR and outcomes were analyzed by quintiles, and secondarily by dichotomizing into <70 or ≥70 beats/min. Patients with cardiogenic shock, intra-aortic balloon pump or inotropic support, and out-of-hospital arrest were excluded. The mean ± SD HR was 70.9 ± 14.7 beats/min. HR by quintile was 55 ± 5, 64 ± 2, 70 ± 1, 77 ± 3, and 93 ± 13 beats/min, respectively. Patients with higher HR were more likely to be women, current smokers, have higher systolic and diastolic blood pressure, atrial fibrillation, recent heart failure, lower ejection fraction, and ST-elevation myocardial infarction as the indication for the PCI (all p ≤0.002). However, rates of treated hypertension, multivessel disease, previous myocardial infarction, PCI, and coronary bypass surgery were lower (all p ≤0.004). Increased HR was associated with higher 30-day mortality (p for trend = 0.04), target vessel revascularization (p for trend = 0.003), and 30-day major adverse cardiac events (MACE) (p for trend = 0.004). In a multivariable analysis, HR was an independent predictor of 30-day MACE (OR 1.21 per quintile; 95% confidence interval (CI): 1.06 to 1.39, p = 0.004). When dichotomized into <70 or ≥70 beats/min, HR independently predicted both 30-day MACE (OR 1.59, 95% CI 1.08 to 2.36, p = 0.02) and 30-day mortality (OR 2.80, 95% CI 1.10 to 7.08, p = 0.03). In conclusion, HR immediately before PCI is an independent predictor of adverse 30-day cardiovascular outcomes.

PMID: 30107905

Nephrol Dial Transplant. 2018 Aug 8.

## Circulating ADAMs are associated with renal and cardiovascular outcomes in chronic kidney disease patients.

Palau V, Riera M, Duran X, Valdivielso JM, Betriu A, Fernández E, Pascual J, Soler MJ.

Background: A disintegrin and metalloproteinase (ADAM) 17, also known as tumour necrosis factor α-converting enzyme (TACE), is a metalloproteinase that releases the ectodomains of most growth factors, cytokines, receptors and enzymes and has been associated with the presence of chronic kidney disease (CKD) and cardiovascular (CV) disease. The role of circulating ADAMs in the progression of renal function and CV events in CKD patients is unknown.

Methods: A total of 2570 subjects from an observational and multicentre study with CKD Stages 3-5, CKD Stage 5D and controls without any history of CV disease were studied. Circulating ADAM activity was assessed using a fluorometric technique. Progression of renal disease was defined as a 30% increase in serum creatinine or dialysis requirement after 24 months of follow-up. CV outcomes were assessed after 48 months of follow-up.

Results: Patients with advanced CKD had higher ADAM activity as compared with patients with moderate CKD or controls. Male patients with progression of CKD had higher ADAM levels at baseline compared with patients with stable renal function {22.19 relative fluorescence units/μL/h [95% confidence interval (CI) 11.22-37.32] versus 12.15 (7.02-21.50)}. After multivariate adjustment, higher ADAM activity was identified as a risk factor for progression of CKD in male patients [30% increase in the creatinine odds ratio (OR) 2.72 (95% CI 1.58-4.68), $P < 0.001$; dialysis requirement OR 3.00 (95% CI 1.65-5.46), $P < 0.001$; dialysis requirement or 30% increase in the creatinine OR 3.15 (95% CI 2.06-4.81), $P < 0.001$]. ADAM activity was also identified as an independent risk factor for CV events [hazard ratio (HR) 1.68 (95% CI 1.20-2.36), $P = 0.003$].

Conclusions: High ADAMs activity levels are independently associated with CKD progression in males and with CV events in CKD patients.

PMID: 30102333

Eur Heart J. 2018 Jul 27.

## Impact of ambulatory cardiac rehabilitation on cardiovascular outcomes: a long-term follow-up study.

Doimo S, Fabris E, Piepoli M, Barbati G, Antonini-Canterin F, Bernardi G, Maras P, Sinagra G.

Aims: To evaluate the long-term clinical impact of the application of cardiac rehabilitation (CR) early after discharge in a real-world population.

Methods and results: We analysed the 5-year incidence of cardiovascular mortality and hospitalization for cardiovascular causes in two populations, attenders vs. non-attenders to an ambulatory CR program which were consecutively discharged from two tertiary hospitals, after ST-elevation myocardial infarction, non-ST-elevation myocardial infarction, coronary artery bypass graft, or planned percutaneous coronary intervention. A primary analysis using multivariable regression model and a secondary analysis using the propensity score approach were performed. Between 1 January 2009 and 31 December 2010, 839 patients attended a CR program planned at discharged, while 441 patients were discharged from Cardiovascular Department without any program of CR. During follow-up, the incidence of cardiovascular mortality was 6% in both groups ($P=0.62$). The composite outcome of hospitalizations for cardiovascular causes and cardiovascular mortality were lower in CR group compared to no-CR group (18% vs. 30%, $P<0.001$) and was driven by lower hospitalizations for cardiovascular causes (15 vs. 27%, $P<0.001$). At multivariable Cox proportional hazard analysis, CR program was independent predictor of lower occurrence of the composite outcome (hazard ratio 0.55, 95% confidence interval 0.43-0.72; $P<0.001$), while in the propensity-matched analysis CR group experienced also a lower total mortality (10% vs. 19%, $P=0.002$) and cardiovascular mortality (9% vs. 35%, $P=0.008$) compared to no-CR group.

Conclusion: This study showed, in a real-world population, the positive effects of ambulatory CR program in improving clinical outcomes and highlights the importance of a spread use of CR in order to reduce cardiovascular hospitalizations and cardiovascular mortality during a long-term follow-up.

PMID: 30060037

J Clin Hypertens (Greenwich). 2018 Sep;20(9):1238-1246.

## Nocturnal blood pressure patterns and cardiovascular outcomes in patients with masked hypertension.

Presta V, Figliuzzi I, D'Agostino M, Citoni B, Miceli F, Simonelli F, Coluccia R, Musumeci MB, Ferrucci A, Volpe M, Tocci G.

Masked hypertension (MHT) is characterized by normal clinic and above normal 24-hour ambulatory blood pressure (BP) levels. We evaluated clinical characteristics and CV outcomes of different nocturnal patterns of MHT. We analyzed data derived from a large cohort of adult individuals, who consecutively underwent home, clinic, and ambulatory BP monitoring at our Hypertension Unit between January 2007 and December 2016. MHT was defined as clinic BP <140/90 mm Hg and 24-hour BP ≥ 130/80 mm Hg, and stratified into three groups according to dipping status: (a) dippers, (b) nondippers, and (c) reverse dippers. From an overall sample of 6695 individuals, we selected 2628 (46.2%) adult untreated individuals, among whom 153 (5.0%) had MHT. In this group, 67 (43.8%) were nondippers, 65 (42.5%) dippers, and 21 (13.7%) reverse dippers. No significant differences were found among groups regarding demographics, clinical characteristics, and prevalence of risk factors, excluding older age in reverse dippers compared to other groups ($P < 0.001$). Systolic BP levels were significantly higher in reverse dippers than in other groups at both 24-hour (135.6 ± 8.5 vs 130.4 ± 6.0 vs 128.2 ± 6.8 mm Hg, respectively; $P < 0.001$) and nighttime periods (138.2 ± 9.1 vs 125.0 ± 6.3 vs 114.5 ± 7.7 mm Hg; $P < 0.001$). Reverse dipping was associated with a significantly higher risk of stroke, even after correction for age, gender, BMI, dyslipidemia, and diabetes (OR 18.660; 95% IC [1.056-33.813]; $P = 0.046$). MHT with reverse dipping status was associated with higher burden of BP and relatively high risk of stroke compared to both dipping and nondipping profiles, although a limited number of CV outcomes have been recorded during the follow-up.

PMID: 30058135

Diabetes Obes Metab. 2018 Jul 23.

## Cardiovascular outcomes of sodium glucose cotransporter-2 inhibitors in patients with type 2 diabetes.

Dawwas GK, Smith SM, Park H

AIMS: To determine the association between cardiovascular diseases (CVD) and SGLT2 inhibitors compared to sulfonylureas and dipeptidyl peptidase-4 (DPP4) inhibitors and to examine within-class effects of SGLT2 inhibitors.
METHODS: A retrospective cohort analysis was conducted using Truven Health MarketScan. New users of SGLT2 inhibitors, sulfonylureas or DPP-4 inhibitors were included. Primary outcome was incident CVD, defined as non-fatal myocardial infarction or non-fatal stroke; secondary outcomes were hospitalization because of heart failure and lower extremity amputation. Proportional hazards models, after propensity score matching, were used to obtain hazard ratios (HR) and 95% confidence intervals (CI).
RESULTS: In fully adjusted models, use of SGLT2 inhibitors was associated with a decreased risk of developing CVD compared with use of sulfonylureas (HR, 0.50; 95% CI, 0.45, 0.55) and DPP-4 inhibitors (HR, 0.57; 95% CI, 0.52, 0.62), respectively. Analyses revealed no evidence of within-class effects: dapagliflozin vs sulfonylureas (HR, 0.55; 95% CI, 0.43, 0.70) or DPP-4 inhibitors (HR, 0.57; 95% CI, 0.46, 0.70); and canagliflozin vs sulfonylureas (HR, 0.61; 95% CI, 0.54, 0.69) or DPP-4 inhibitors (HR, 0.66; 95% CI, 0.54, 0.71). Additionally, SGLT2 inhibitors were associated with lower risk of hospitalization because of heart failure compared to both sulfonylureas and DPP-4 inhibitors, as well as lower risk of lower extremity amputation compared to sulfonylureas.
CONCLUSION: Using population-based data, incident use of SGLT-2 inhibitors was associated with a decreased incidence of CVD compared to use of sulfonylureas and DPP-4 inhibitors. These findings were consistent between dapagliflozin and canagliflozin, suggesting that CVD reduction is a class effect for SGLT2 inhibitors. In addition, SGLT2 inhibitors portended lower risk of hospitalization because of heart failure (vs sulfonylureas and DPP-4 inhibitors) and lower risk of lower extremity amputation (vs sulfonylureas).

PMID: 30039524

Atherosclerosis. 2018 Jul 6. pii: S0021-9150(18)31201-2.

## High-density lipoprotein function is associated with atherosclerotic burden and cardiovascular outcomes in type 2 diabetes.

Heier M, Ofstad AP, Borja MS, Brunborg C, Endresen K, Gullestad L, Birkeland KI, Johansen OE, Oda MN.

BACKGROUND AND AIMS: Measures of HDL function are emerging tools for assessing cardiovascular disease (CVD) event risk. HDL-apoA-I exchange (HAE) reflects HDL capacity for reverse cholesterol transport.
METHODS: HAE was measured in 93 participants with type 2 diabetes (T2D) and at least one additional CVD risk factor in the Asker and Bærum Cardiovascular Diabetes study. At baseline and after seven years, the atherosclerotic burden was assessed by invasive coronary angiography. Major CVD events were registered throughout the study.
RESULTS: Linear regression analysis demonstrated a significant inverse association between HAE and atherosclerotic burden. Cox proportional hazard regression analysis showed a significant association between HAE and a composite of major CVD events when controlling for waist-hip ratio, HR = 0.89, 95% CI = 0.80-1.00 and p=0.040.
CONCLUSIONS: Despite the relatively small size of the study population and the limited number of CVD events, these findings suggest that HAE provides valuable information in determining CVD risk.

PMID: 30017177

Medicine (Baltimore). 2018 Jul;97(28):e11517.

## Change in lipoprotein-associated phospholipase A2 and its association with cardiovascular outcomes in patients with acute coronary syndrome.

Li J, Wang H, Tian J, Chen B, Du F.

Lipoprotein-associated phospholipase A2 (Lp-PLA2) probably plays an important role in the development of acute coronary syndrome (ACS). However, alterations of Lp-PLA2 levels during ACS and its association with cardiovascular outcome are unclear. Our aim was to investigate the change in Lp-PLA2 and its association with cardiovascular outcome in patients with ACS.A total of 79 patients with ACS came from the coronary care unit (CCU) between June 1, 2015 and August 31, 2016 in this longitudinal study. Serum levels of Lp-PLA2, troponin I, and creatine kinase isoenzymes MB (CK-MB) were measured at admission, on the first morning (D1), on the second morning of hospitalization (D2), and on the last second morning before discharge (D4). The patients were followed up till November 30, 2016. The primary outcomes were cardiovascular death and cardiovascular rehospitalization. Kaplan-Meier analysis and Cox proportional hazard models were used to identify risk factors for poor outcome in patients with ACS.All patients were followed up for 10.6±4.7 months. The patients were divided into 2 groups according to the median of Lp-PLA2: lower Lp-PLA2 group and higher Lp-PLA2 group. Elevated levels of Lp-PLA2 significantly decreased during the early phases of ACS in higher Lp-PLA2 group. And Lp-PLA2 level increased at first and then decreased in lower Lp-PLA2 group. Kaplan-Meier analysis showed that patients with elevated Lp-PLA2 had a lower cardiovascular event-free survival (log-rank $\chi$=4.736, P=.030) than those with lower Lp-PLA2. Cox regression analysis indicated that high Lp-PLA2 level (hazard ratio [HR]=1.005, 95% confidence interval [CI]=1.002-1.008, P=.003), time delay from symptom onset to admission (HR=1.088, 95% CI=1.038-1.139, P<.001) independently predicted cardiovascular event in patients with ACS after adjusting for potential confounders.Serum level of Lp-PLA2 altered considerably during the early phase of ACS and increased Lp-PLA2 independently predicted cardiovascular outcome in patients with ACS after adjustment for potential confounders.

PMCID: PMC6076090
PMID: 29995820 [Indexed for MEDLINE]

Kidney Int Rep. 2018 Apr 16;3(4):939-949.

## Change in Albuminuria and Risk of Renal and Cardiovascular Outcomes: Natural Variation Should Be Taken into Account.

Smith M, Herrington WG, Weldegiorgis M, Hobbs FR, Bankhead C, Woodward M.

Introduction: Changes in urinary albumin-to-creatinine ratio (UACR) may affect the risk of advanced chronic kidney disease (CKD). How much the association changes after taking account for natural variation in UACR and the length of time taken to observe changes in UACR is unknown.

Methods: English Clinical Practice Research Datalink records (2000-2015) with linkage to secondary care and death certification were used to identify prospective cohorts with at least 2 measures of UACR within 1, 2, and 3 years. Adjusted Cox regression assessed the separate relevance of the baseline UACR and the UACR change to the risk of developing stages 4 to 5 CKD and end-stage renal disease (ESRD). Associations were compared before and after accounting for the effects of the natural variation in UACR (i.e., regression to the mean).

Results: A total of 212,810 individuals had baseline UACR measurements; 22% had a UACR ≥3.4 mg/mmol, and 3% had UACR ≥33.9 mg/mmol. During a median 4-year follow-up, 5976 developed stage 4 to 5 CKD, and 1076 developed ESRD. There were strong associations between baseline UACR and stage 4 to 5 CKD or ESRD risk, which doubled in strength after accounting for regression to the mean. Over 3 years, the hazard ratios (95% confidence intervals) for stage 4 to 5 CKD, relative to stable UACR, were 0.62 (0.50-0.77) for at least a halving of UACR and 2.68 (2.29-3.14) for at least a doubling of UACR. Associations were weaker for shorter exposure windows (and for cardiovascular disease or death), but strengthened after allowing for regression to the mean.

Conclusion: Baseline values and subsequent medium-term increases in albuminuria are both associated with substantially increased risk of developing advanced CKD. Standard analyses, not allowing for natural variation in UACR, may underestimate these associations.

PMCID: PMC6035156
PMID: 29988998

J Clin Hypertens (Greenwich). 2018 Sep;20(9):1247-1252.

## Blood pressure variability predicts adverse events and cardiovascular outcomes in SPRINT.

Mezue K, Goyal A, Pressman GS, Matthew R, Horrow JC, Rangaswami J.

SPRINT (Systolic Blood Pressure Intervention Trial) highlighted the benefits of intensive targeted antihypertensive therapy but resulted in higher rates of treatment-related adverse events. Blood pressure (BP) variability has emerged as a significant predictor of outcomes over and above levels of BP. Using the SPRINT data set, we aimed to determine the relationship of BP variability with cardiovascular outcomes and side effects of antihypertensive therapy. The analyses included all participants randomized in SPRINT who reached the target systolic BP (SBP) for their respective groups (intensive < 120 mm Hg; standard < 140 mm Hg). Coefficients of variation (CV) for SBP, diastolic BP (DBP), and PP for each patient characterized variability. Student t test was used to compare treatment arms for each CV metric. Cox proportional hazards regression was used to identify independent predictors of the SPRINT primary outcome and adverse events. P < .15 on univariate analysis was required to enter the model and P < .05 to remain in it. A total of 8884 patients (4561 standard group; 4323 intensive group) met inclusion criteria. DBP CV differed between the groups (9.12 ± 3.20 standard group; 9.47 ± 3.49 intensive group [P < .0001]). DBP CV predicted a greater hazard for the primary outcome (hazard ratio [HR], 1.14) in the overall model as well as separate analyses by treatment arms (standard group HR, 1.15; intensive group HR, 1.19), each P < .0001. DBP CV also independently predicted a greater hazard for acute kidney injury (HR, 1.12) and hypotensive events (HR, 1.12). Visit-to-visit DBP variability independently predicted worse cardiovascular outcomes and hypoperfusion-related adverse events in SPRINT.

PMID: 29984884

Diabetes Res Clin Pract. 2018 Sep;143:34-42.

## Cardiovascular safety of GLP-1 receptor agonists for diabetes patients with high cardiovascular risk: A meta-analysis of cardiovascular outcomes trials.

Wang Q, Liu L, Gao L, Li Q.

AIM: To show long-term cardiovascular safety of the GLP-1 receptor agonists for diabetes patients with cardiovascular risk.
METHODS: For cardiovascular outcomes, the association between treatment and outcomes was estimated using the odds ratio and 95% confidence interval. I2 test was adopted to assess the magnitude of heterogeneity between studies, with values more than 25%, 50%, and 75% defined as low, moderate, or high heterogeneity.
RESULTS: We combined data from four cardiovascular outcomes trials and prospectively blinded endpoint adjudication. 4105 cardiovascular events including cardiovascular death, acute MI or stroke experienced during the trials. And the odds ratios of the cardiovascular outcomes were 0.90 (95% CI 0.81, 1.00) for the cardiovascular outcome, 0.93 (95% CI 0.85, 1.02) for nonfatal myocardial infarction, 0.88 (95% CI 0.76, 1.03) for nonfatal stroke, 0.94 (95% CI 0.84, 1.05) for heart failure hospitalization, 0.89 (95% CI 0.63, 1.27) for pancreatitis, 0.98 (95% CI 0.92, 1.05) for any hypoglycemic events, 0.92 (95% CI 0.83, 1.01) for the severe hypoglycemic events, 0.96 (95% CI 0.83, 1.01) for serious adverse events. Significant differences showed in mortality parameters: 0.88 (95% CI 0.81, 0.95) for all-cause mortality, 0.87 (95% CI 0.79, 0.97) for cardiovascular mortality. CV benefits were obtained in the male, black, Asian patients and patients with BMI ≥ 30 kg/m2.
CONCLUSION: Additional GLP-1 receptor agonists treatment did not increase cardiovascular outcomes in diabetes patients with high cardiovascular risk or established cardiovascular disease.

PMID: 29935211

Diabetes Care. 2018 Aug;41(8):1792-1800

## Adiponectin, Free Fatty Acids, and Cardiovascular Outcomes in Patients With Type 2 Diabetes and Acute Coronary Syndrome.

Schrieks IC, Nozza A, Stähli BE, Buse JB, Henry RR, Malmberg K, Neal B, Nicholls SJ, Rydén L, Mellbin L, Svensson A, Wedel H, Weichert A, Lincoff AM, Tardif JC, Grobbee DE, Schwartz GG.

OBJECTIVE: In observational cohorts, adiponectin is inversely associated and free fatty acids (FFAs) are directly associated with incident coronary heart disease (CHD). Adiponectin tends to be reduced and FFAs elevated in type 2 diabetes. We investigated relationships of adiponectin and FFA and major adverse cardiovascular events (MACEs) and death in patients with acute coronary syndrome (ACS) and type 2 diabetes using data from the AleCardio (Effect of Aleglitazar on Cardiovascular Outcomes After Acute Coronary Syndrome in Patients With Type 2 Diabetes Mellitus) trial, which compared the PPAR-α/γ agonist aleglitazar with placebo.

RESEARCH DESIGN AND METHODS: Using Cox regression adjusted for demographic, laboratory, and treatment variables, we determined associations of baseline adiponectin and FFAs, or the change in adiponectin and FFAs from baseline, with MACEs (cardiovascular death, myocardial infarction, or stroke) and death.

RESULTS: A twofold higher baseline adiponectin (n = 6,998) was directly associated with risk of MACEs (hazard ratio [HR] 1.17 [95% CI 1.08-1.27]) and death (HR 1.53 [95% CI 1.35-1.73]). A doubling of adiponectin from baseline to month 3 (n = 6,325) was also associated with risk of death (HR 1.20 [95% CI 1.03-1.41]). Baseline FFAs (n = 7,038), but not change in FFAs from baseline (n = 6,365), were directly associated with greater risk of MACEs and death. There were no interactions with study treatment.

CONCLUSIONS: In contrast to prior observational data for incident CHD, adiponectin is prospectively associated with MACEs and death in patients with type 2 diabetes and ACS, and an increase in adiponectin from baseline is directly related to death. These findings raise the possibility that adiponectin has different effects in patients with type 2 diabetes and ACS than in populations without prevalent cardiovascular disease. Consistent with prior data, FFAs are directly associated with adverse outcomes.

PMID: 29903845 [Indexed for MEDLINE]

Expert Opin Drug Saf. 2018 Jul;17(7):697-708.

## Cardiovascular outcomes of patients with rheumatoid arthritis prescribed disease modifying anti-rheumatic drugs: a review.

Giollo A, Bissell LA, Buch MH.

INTRODUCTION: Rheumatoid arthritis (RA) is associated with a heightened risk of cardiovascular disease (CVD), with both traditional CV risk factors and inflammation contributing to this risk. Areas covered: This review highlights the burden of CVD in RA and associated traditional CV risk factors, including the complexity of dyslipidemia in RA and the so-called 'lipid paradox.' Furthermore, the recognized RA-disease-specific factors associated with higher risk of CVD and the role of systemic inflammation in the pathogenesis of CVD in RA will be addressed. With the advent of biologic and targeted synthetic therapies in the treatment of RA, the effect of conventional and newer generation disease modifying anti-rheumatic therapies (DMARDs) on CV risk and associated risk factors will also be discussed. Expert opinion: Identifying the RA phenotype at greatest risk of CVD, understanding the interplay of increased traditional risk factors, common inflammatory processes and RA-specific factors, and personalized use of DMARDs according to disease phenotype and comorbidity to reduce this risk are key areas for future research.

PMID: 29871535 [Indexed for MEDLINE]

J Am Geriatr Soc. 2018 Sep;66(9):1805-1811.

## Cardiovascular Outcomes of Cholinesterase Inhibitors in Individuals with Dementia: A Meta-Analysis and Systematic Review.

Isik AT, Soysal P, Stubbs B, Solmi M, Basso C, Maggi S, Schofield P, Veronese N, Mueller C.

OBJECTIVES: To evaluate the cardiovascular (CV) effects of acetylcholinesterase inhibitors (AChEIs) in individuals with dementia DESIGN: Systematic review and meta-analysis.
SETTING: Two authors independently searched major electronic databases from inception until June 17, 2017, for longitudinal (without a control group) and cohort (with a control group) studies reporting CV outcomes in relation to AChEIs. Randomized controlled trials were excluded because they included relatively healthy subjects.
PARTICIPANTS: Individuals with dementia and controls.
MEASUREMENTS: Changes in CV parameters were summarized using standardized mean differences (SMDs) with 95% confidence intervals (CIs). Event rates were used to assess incidence of hypertension and bradycardia. Incidence of CV events in demented patients versus in healthy controls were compared using hazard ratios (HRs).
RESULTS: Of 4,588 initial hits, 31 studies including 258,540 individuals with dementia and 2,246,592 controls were analyzed. In longitudinal and open-label studies, AChEIs were associated with a significantly greater incidence of hypertension (n=1,573, 4%, 95% CI=2-8%, I2 =47%) and bradycardia (n=13,703, 2%, 95% CI=1-6%, I2 =98%). AChEIs were associated with a decrease in heart rate (SMD=-1.77, 95% CI=-3.58-0.03, I2 =78%) and an increase in PR interval (SMD=0.10, 95% CI=0.008-0.19, I2 =3%) from baseline. During a median follow-up of 116 weeks, AChEIs were associated with a significantly lower risk of CV events (stroke, acute coronary syndrome, CV mortality; HR=0.63, 95% CI=0.45-0.88, I2 =18%), without a significantly greater risk of bradycardic events (HR=1.40, 95% CI=0.76-2.59, I2 =98%).
CONCLUSION: AChEI therapy may be associated with negative chronotropic and hypertensive effects but also with lower risk of CV events.

PMID: 29851022

Diabetes Care. 2018 Jul;41(7):1510-1515.

## Serial Measurement of Natriuretic Peptides and Cardiovascular Outcomes in Patients With Type 2 Diabetes in the EXAMINE Trial.

Jarolim P, White WB, Cannon CP, Gao Q, Morrow DA.

OBJECTIVE: Patients with type 2 diabetes are at increased risk of developing heart failure (HF). Enhanced recognition of patients at risk for HF would help guide therapeutic decisions.
RESEARCH DESIGN AND METHODS: We investigated the prognostic implications of changes in N-terminal B-type natriuretic peptide (NT-proBNP) concentration in patients with type 2 diabetes and ischemic heart disease who were enrolled in the Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care (EXAMINE) trial, a phase 3b trial of alogliptin, a dipeptidyl peptidase 4 (DPP-4) inhibitor. Patients with type 2 diabetes and a recent acute coronary syndrome event were eligible. NT-proBNP was measured at baseline and 6 months. Cardiovascular (CV) death or hospitalization for HF was the end point of principal interest for this analysis.
RESULTS: We observed a strong graded relationship between increasing baseline and 6-month NT-proBNP concentration and the incidence of major CV events ($P < 0.001$). After adjusting for potential confounders, NT-proBNP at baseline was independently associated with the development of major CV events, in particular hospitalization for HF. Patients who had persistently high NT-proBNP ($P < 0.001$) or developed high NT-proBNP at 6 months ($P < 0.001$) were at a significantly higher risk for CV death/HF than those in whom NT-proBNP remained low at both time points or who had a high NT-proBNP value at baseline that subsequently declined to the low category. Absolute changes in NT-proBNP by 6 months were also strongly associated with subsequent outcomes. Treatment with a DPP-4 inhibitor did not meaningfully alter NT-proBNP concentrations ($P = 0.20$).
CONCLUSIONS: Serial monitoring of NT-proBNP in patients with type 2 diabetes and ischemic heart disease may be useful for identifying patients at highest risk for HF.

PMID: 29848776 [Indexed for MEDLINE]

J Hypertens. 2018 Aug;36(8):1637-1647.

## Effects of blood pressure-lowering treatment on cardiovascular outcomes and mortality: 14 - effects of different classes of antihypertensive drugs in older and younger patients: overview and meta-analysis.

Thomopoulos C, Parati G, Zanchetti A.

BACKGROUND AND OBJECTIVES: The five major classes of blood pressure (BP)-lowering drugs have all been shown to significantly reduce the risk of major cardiovascular events when compared with placebo, and when directly (head-to-head) compared, no significant differences in their overall effectiveness have been detected, except for minor differences in cause-specific events. It is unknown, however, whether age-related differences exist and if some classes of drugs are differently effective in older or younger individuals. This clinically relevant question has been the object of a systematic search and meta-analysis of all available data. METHODS: Two databases we had previously identified [72 placebo-controlled BP-lowering randomized clinical trials (RCTs) in 260210 individuals and 50 RCTs head-to-head comparing treatments with BP-lowering drugs of different classes in 247006 individuals) were searched for separately reported data on patients older or younger than 65 years, and the data were further stratified according to the class of drug [diuretics, beta-blockers, calcium antagonists, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers] compared with placebo or with other drug classes. Seven fatal and nonfatal outcomes were considered for benefits. Adverse events were investigated as permanent treatment discontinuations for adverse events. Risk ratios and absolute risk changes were calculated by a random effects model. Effects at older and younger ages were compared by heterogeneity test. RESULTS: We identified 20 placebo-controlled RCTs on 55645 older individuals and 21 on 99621 younger individuals, and 21 head-to-head drug comparison RCTs on 94228 older individuals and 27 on 100232 younger individuals (for a total of 349726 individuals). When compared with placebo, all five classes of BP-lowering drugs significantly reduced the risk of major cardiovascular events or stroke, with no significant difference between older and younger patients. However, in head-to-head comparisons, no significant difference was found between older and younger patients in the effects of diuretics, calcium antagonists, ACE inhibitors and angiotensin receptor blockers on all cardiovascular outcomes, whereas beta-blockers revealed an age-dependent effectiveness, being equally effective as the other agents at an age below 65 years, but less effective at an older age. CONCLUSION: Most BP-lowering classes are equally effective in preventing risk of fatal and nonfatal cardiovascular events both in older and younger patients, whereas beta-

blockers, though being equally effective as the other agents in patients younger than 65, loose some of their effectiveness at an older age.

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# Effects of blood pressure-lowering treatment on cardiovascular outcomes and mortality: 13 - benefits and adverse events in older and younger patients with hypertension: overview, meta-analyses and meta-regression analyses of randomized trials.

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BACKGROUND: There is overwhelming evidence that blood pressure (BP)-lowering treatment can reduce cardiovascular outcomes also in the elderly, but some important aspects influencing medical practice are controversial as sufficient evidence has not been provided by single randomized controlled trials (RCTs), whereas evidence may result from a systematic search and meta-analysis of all available data. OBJECTIVES: The following clinically relevant issues concerning the effects of BP lowering in older and younger individuals have been investigated: differences in benefits; the oldest and the youngest age range for which evidence of BP-lowering effects is available; the SBP level at which BP-lowering treatment should be initiated; the SBP and DBP levels treatment should be aimed at; differences in treatment burdens and harms.

METHODS: A database we previously identified of 72 BP-lowering RCTs in 260210 patients was searched for separately reported data on older and younger individuals [cutoffs of 65 (primary analyses), 70, 75, 80, 60 and 55 years). The data were further stratified according to the levels of baseline (untreated) BP, and of on-treatment achieved SBP or DBP. Seven fatal and nonfatal outcomes were considered for benefits. Burdens and harms were investigated as permanent treatment discontinuations for adverse events, and hypotension/syncope. Risk ratios and absolute risk changes were calculated by a random effects model. Effects at older and younger ages were compared by heterogeneity test.

RESULTS: Thirty-two RCTs provided data on 96549 patients older than 65 years, and 31 RCTs on 114009 patients younger than 65 years. All cardiovascular outcomes were significantly reduced by treatment both in older and younger individuals, without significant age-dependent differences in relative risk reduction but with significantly higher absolute risk reductions in older individuals. The extreme age ranges for which evidence of significant benefits of treatment were available was greater than 80 and less than 55 years. Only one RCT provided data on benefits of BP-lowering at age greater than 65 when treatment was initiated at SBP values in the grade 1 range, but more consistent evidence was provided when age was greater than 60 years. Both in patients older and younger than 65 years, significant reductions of cardiovascular outcomes were found at on-treatment SBP less than 140mmHg and DBP less than 80mmHg. There was no evidence that treatment discontinuations for adverse events or hypotension/syncope were more frequent at age greater than 65.

CONCLUSION: Antihypertensive treatment should be recommended to all individuals with elevated BP, independent of age. The prudent recommendation to initiate treatment at SBP values 140-159mmHg is supported at older age defined as greater than 60 years. SBP and DBP values lower than 140mmHg and, respectively, 80mmHg can be aimed at with incremental benefits without disproportionate burdens until age 80 years, above which available evidence is for benefits at on-treatment SBP 140-149mmHg. PMID: 29847485