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

Risco Cardiovascular

Ann Med. 2018;50(sup1):S1-S9.

AFM as a tool to evaluate the risk for cardiovascular diseases in patients.

Guedes AF, Sargento L, Braz-Nogueira J, Lousada N, Moreira C, Carvalho FA, Santos NC

Erythrocyte aggregation is an indicator of cardiovascular risk, which is influenced by plasma fibrinogen concentration. Fibrinogen levels are elevated during cardiovascular diseases. Our main goals were to understand how fibrinogen-erythrocyte binding influences erythrocyte aggregation and how it constitutes a cardiovascular risk factor in essential arterial hypertension (EAH) and chronic heart failure (CHF). Fibrinogen-erythrocyte and erythrocyte-erythrocyte adhesion measurements were conducted by atomic force microscopy (AFM)-based force spectroscopy. Upon increasing fibrinogen concentration, there was an increase in the work and force necessary for cell-cell detachment, both for healthy donors and EAH patients. Nevertheless, higher values were obtained for the EAH patients at each fibrinogen concentration. Fibrinogen-erythrocyte (un)binding forces were higher in EAH and CHF patients, when compared with the control group, despite a lower binding frequency. Ischemic CHF patients showed increased binding forces compared to non-ischemic patients. Erythrocyte deformability (assessed as elongation index) results show that heart failure patients presented higher erythrocyte deformability than the control group at lower shear stresses, and lower deformability at higher shear stresses. This indicates that patients' erythrocytes are more deformable than those from healthy donors in blood vessels with larger internal diameters; however, in smaller-diameter vessels the opposite trend exists. Finally, a 12-month clinical follow-up shows that CHF patients with higher fibrinogen-erythrocyte binding forces, probed by AFM at the beginning of the assessment, had a significantly higher probability of being hospitalized due to cardiovascular complications on the subsequent year. Our results show that AFM can be a promising tool for clinical prognosis, pinpointing those patients with increased risk for cardiovascular diseases.

PMID: 29676178

Semin Arthritis Rheum. 2018 Mar 17. pii: S0049-0172(17)30621-2.

Cardiovascular risk factors predicting cardiac events are different in patients with rheumatoid arthritis, psoriatic arthritis, and psoriasis.

Cooksey R, Brophy S, Kennedy J, Gutierrez FF, Pickles T, Davies R, Piguet V, Choy E

OBJECTIVES: Increased cardiovascular risk in rheumatoid arthritis (RA) is well established. Examining traditional cardiovascular risk factors alone underestimates cardiovascular risk in RA. Systematic inflammation, measured by erythrocyte sedimentation rate or C-reactive protein is also a major risk factor. However, the contribution of traditional cardiovascular risk factors (such as obesity and hyperlipidaemia) compared to inflammation is uncertain in psoriatic arthritis (PsA) and RA. We examine the incidence of major adverse cardiac events (MACE) among patients with RA, PsA psoriasis, and controls adjusting for risk factors, inflammation and disease modifying anti-rheumatic drug treatment, to better define cardiovascular risk.
METHODS: Using the Secure Anonymised Information Linkage databank, comprising routinely collected Welsh health data from 1999 to 2013, the incidence and first occurrence of a MACE in individuals with RA (n = 8650), PsA (n = 2128) and psoriasis (n = 24,630) compared to controls (n = 11,87,706) was investigated.
RESULTS: Traditional cardiovascular risk factors are higher in RA, PsA and psoriasis than controls. After adjusting for these factors, additional cardiovascular risk was only significantly increased in female RA patients (HR = 1.3; 95% CI: 1.0-1.7; p = 0.05) and psoriasis (HR = 1.2; 95% CI: 1.0-1.4; p = 0.02) but not statistically significant for PsA (HR = 1.5; 95% CI: 0.9-2.5; p = 0.13). ESR and CRP were increased in patients with RA but not in patients with psoriasis.
CONCLUSION: Additional increased cardiovascular risk was observed in female RA and psoriasis but not PsA. Systematic inflammation is higher in RA but not psoriasis, indicating that there are varying mediators of cardiovascular risk across these conditions.

PMID: 29656791

Cardiovasc Diabetol. 2018 Mar 29;17 (1):46.

The role of obesity in carotid plaque instability: interaction with age, gender, and cardiovascular risk factors.

Rovella V, Anemona L, Cardellini M, Scimeca M, Saggini A, Santeusanio G, Bonanno E, Montanaro M, Legramante IM, Ippoliti A, Di Daniele N, Federici M, Mauriello A.

BACKGROUND: In the last decade, several studies have reported an unexpected and seemingly paradoxical inverse correlation between BMI and incidence of cardiovascular diseases. This so called "obesity paradox effect" has been mainly investigated through imaging methods instead of histologic evaluation, which is still the best method to study the instability of carotid plaque. Therefore, the purpose of our study was to evaluate by histology the role of obesity in destabilization of carotid plaques and the interaction with age, gender and other major cerebrovascular risk factors.

METHODS: A total of 390 carotid plaques from symptomatic and asymptomatic patients submitted to endarterectomy, for whom complete clinical and laboratory assessment of major cardiovascular risk factors was available, were studied by histology. Patients with a BMI ≥30.0 kg/m2 were considered as obese. Data were analyzed by multivariate logistic regression and for each variable in the equation the estimated odds ratio (OR) was calculated.

RESULTS: Unstable carotid plaque OR for obese patients with age <70 years was 5.91 (95% CI 1.17-29.80), thus being the highest OR compared to that of other risk factors. Unstable carotid plaque OR decreased to 4.61 (95% CI 0.54-39.19) in males ≥70 years, being only 0.93 (95% CI 0.25-3.52) among women. When obesity featured among metabolic syndrome risk factors, the OR for plaque destabilization was 3.97 (95% CI 1.81-6.22), a significantly higher value compared to OR in non-obese individuals with metabolic syndrome (OR=1.48; 95% CI 0.86-2.31). Similar results were obtained when assessing the occurrence of acute cerebrovascular symptoms.

CONCLUSIONS: Results from our study appear to do not confirm any paradoxical effect of obesity on the carotid artery district. Conversely, obesity is confirmed to be an independent risk factor for carotid plaque destabilization, particularly in males aged <70 years, significantly increasing such risk among patients with metabolic syndrome.

PMCID: PMC5874994
PMID: 29598820

Eur J Prev Cardiol. 2018 Jan 1:2047487318766638

Ambient air pollution and cardiovascular diseases: From bench to bedside.

Vidale S, Campana C.

Air pollution has a great impact on health, representing one of the leading causes of death worldwide. Previous experimental and epidemiological studies suggested the role of pollutants as risk factors for cardiovascular diseases. For this reason, international guidelines included specific statements regarding the contribution of particulate matter exposure to increase the risk of these events. In this review, we summarise the main evidence concerning the mechanisms involved in the processes linking air pollutants to the development of cardiovascular diseases.

PMID: 29580063

Am J Med. 2018 Mar 22. pii: S0002-9343(18)30101-3.

Improved Cardiovascular Risk Factors Control Associated with a Large-Scale Population Management Program Among Diabetes Patients.

Rana JS, Karter AJ, Liu JY, Moffet HH, Jaffe MG

BACKGROUND: Optimal cardiovascular risk factors control among individuals with diabetes remains a challenge. We evaluated changes in glucose, lipid, and blood pressure control among diabetes patients after implementation of a large-scale population management program, known as Preventing Heart Attacks and Strokes Everyday, at Kaiser Permanente Northern California (KPNC), during 2004-2013.
METHODS: We used National Committee for Quality Assurance Healthcare Effectiveness Data and Information Set cut points to identify prevalence of poor glycemic (hemoglobin A1c > 9%) control, good lipid control (low-density lipoprotein cholesterol < 100 mg/dL), and good blood pressure control (blood pressure < 140/90 mm Hg) in each year (N range = 98,345 to 122,177 over the entire period). We assessed trends in risk factor control based on Joinpoint regression and average annual percentage change (AAPC) compared with published National Committee for Quality Assurance Healthcare Effectiveness Data and Information Set commercial rates.
RESULTS: We found that the prevalence of poor glycemic control (hemoglobin A1c > 9%) declined in both KPNC and nationally, but was statistically significant only in KPNC (AAPC = -4.8; P < .05). The prevalence of good lipid control (low-density lipoprotein cholesterol < 100 mg/dL) increased significantly in KPNC (47% to 71%; AAPC = +4.3; P < .05), but there was no significant improvement nationally (40% to 44%; AAPC = +1.4; P = .2). The prevalence of blood pressure control (<140/90 mm Hg) was higher in KPNC (77% to 82%; AAPC = +1.1; P < .05) versus nationally (57% to 62%; AAPC = +1.9; P < .05) during the reported years 2007-2013.
CONCLUSIONS: Relative to national benchmarks, a substantially greater improvement in risk factor control among adults with diabetes was observed after implementation of a comprehensive population management program.

PMID: 29576192

Curr Atheroscler Rep. 2018 Mar 20;20 (5):23.

Assessing Cardiovascular Disease Risk and Responses to Preventive Therapies in Clinical Practice.

Maki KC, Dicklin MR.

PURPOSE OF REVIEW: The aims of this review are to provide perspective on evaluation of relative and absolute cardiovascular disease (CVD) risk reductions for assessing the efficacy of preventive therapies and to summarize methods for evaluation of CVD risk in clinical practice. RECENT FINDINGS: Major CVD risk factors can be used to stratify patients into risk categories. Results from recent trials reinforce the view that benefits of preventive therapies will be greatest in those with the highest absolute risk and in those with the most severe disturbance in the risk factor targeted. In evaluating clinical utility, it is necessary to assess the impact of an intervention on both relative and absolute risk. Quantitative risk scoring using major CVD risk factors is effective for identifying those at low, moderate, and high CVD risk. When there is uncertainty about the appropriate treatment strategy, additional testing may be used to refine risk assessment. This may include measurement of inflammatory markers, subclinical indicators of atherosclerosis (e.g., coronary artery calcium and ankle brachial index), urinary albumin/creatinine ratio, and the level of lipoprotein (a). The benefit of a preventive therapy will generally be the greatest in those with the highest absolute risk and in those with the most severe disturbance in the risk factor targeted. Quantitative risk scoring with major CVD risk factors can be supplemented with additional testing for refinement of risk assessment in patients for whom decisions about pharmacotherapy, or the intensity of therapy, for risk factor modification are uncertain.

PMID: 29556802

Ann Cardiol Angeiol (Paris). 2018 Apr;67(2):82-90.

[Serum albumin and cardiovascular diseases: A comprehensive review of the literature].

[Article in French]

Arques S

Cardiovascular diseases are the leading cause of death worldwide. Conceptually, endothelial dysfunction, inflammatory status and oxidative stress are at the forefront in the onset and development of most cardiovascular diseases, particularly coronary artery disease and heart failure. Serum albumin, the most abundant plasma protein, has many physiological properties, including anti-inflammatory, antioxidant and antiplatelet aggregation activity. It also plays an essential role in the fluid exchange across the capillary membrane. Definite evidence is that hypo-albuminemia is a powerful prognostic marker in the general population as well as in many pathological settings. In the more specific context of cardiovascular diseases, serum albumin is independently associated with the development of a variety of deleterious conditions such as coronary artery disease, heart failure, atrial fibrillation and stroke. Serum albumin has also emerged as a powerful prognostic parameter in patients with coronary artery disease, heart failure, congenital heart disease, infective endocarditis, cardiovascular surgery and stroke, regardless of usual prognostic markers. This prognostic value probably refers mainly to the malnutrition-inflammation syndrome and the severity of comorbidities. Nevertheless, hypo-albuminemia may act as an unknown and modifiable risk factor that contributes to the emergence and the pejorative evolution of cardiovascular diseases, mainly by exacerbation of inflammation, oxidative stress and platelet aggregation, and by pulmonary and myocardial edema. This article provides an overview of the physiological properties of serum albumin, the prevalence, causes, prognostic value and potential contribution to the emergence and aggravation of cardiovascular disease of hypoalbuminemia, as well as its clinical implications.

PMID: 29544976

Nutr Res. 2018 Feb;50: 63-72.

Antioxidants from diet or supplements do not alter inflammatory markers in adults with cardiovascular disease risk. A pilot randomized controlled trial.

Dewell A, Tsao P, Rigdon J, Gardner CD.

Antioxidants have been reported to have anti-inflammatory effects, but there is a lack of research comparing food to supplement antioxidant sources. The aim of this study was to determine if increases in intake of foods naturally rich in antioxidants would lower blood levels of inflammatory markers more than consuming antioxidant supplements among adults with cardiovascular disease risk factors. Eighty-eight generally healthy adults with ≥1 elevated risk factor for cardiovascular disease were randomized in a single-blind (diets)/double-blind (supplements), parallel-group study for 8 weeks. Participants consumed (1) usual diet and placebo pills (n = 29), (2) usual diet and antioxidant supplements (n = 29), or (3) antioxidant-rich foods closely matched to antioxidant content of supplements and placebo (n = 30). Usual diet combined with antioxidant supplements or increased antioxidant-rich food intake was designed to approximately double daily habitual antioxidant intake. Antioxidant pills included carotenoids, mixed tocopherols, vitamin C, and selenium. Fasting blood samples were analyzed for inflammatory marker concentrations of interleukin-6, monocyte chemotactic protein-1, and soluble intercellular adhesion molecule-1. Participants in the intervention groups successfully doubled most antioxidants as verified by diet records and elevated blood concentrations in treatment groups. Baseline levels of inflammatory markers for the entire study group were 110 ± 65 pg/mL for monocyte chemotactic protein-1, 0.9 ± 0.7 pg/mL for interleukin-6, and 217 ± 56 ng/mL for soluble intercellular adhesion molecule-1 (means ± standard deviation) and did not differ by treatment arm. After 8 weeks, there were no significant within-group changes or between-group 8-week change differences in inflammatory marker concentrations. In conclusion, no beneficial effects were detected on the inflammatory markers investigated in response to antioxidants from foods or supplements.

PMCID: PMC5858717 [Available on 2019-02-01]
PMID: 29540273

Postgrad Med. 2018 Apr;130(3):317-324

Comorbidities and cardiovascular risk factors in an aged cohort of HIV-infected patients on antiretroviral treatment in a Spanish hospital in 2016.

Fontela C, Castilla J, Juanbeltz R, Martínez-Baz I, Rivero M, O'Leary A, Larrea N, San Miguel R

OBJECTIVES: The increased survival of HIV-infected individuals has resulted in a premature aging of this population, with the consequent development of premature age-related comorbidities and risk factors. We aimed to describe the prevalence of age-related comorbidities and cardiovascular risk factors in older adults with HIV infection on antiretroviral therapy (ART).

METHODS: A retrospective cross-sectional study was undertaken in a cohort of HIV patients aged ≥50 years on ART in September 2016 in Spain. The prevalence of comorbidities (liver cirrhosis, respiratory diseases, cancer, cardiovascular, diabetes, and kidney and bone disorders) and risk factors (smoking, dyslipidemia, and arterial hypertension) was captured.

RESULTS: Among the 339 patients included in the study, any comorbidity was present in 52%, the most common being cirrhosis (19%), chronic lung disease (13%), and diabetes mellitus (11%). Over three quarters (78%) had any risk factor: dyslipidemia (55%) and smoking (44%). A higher prevalence of cardiovascular disease was seen in patients ≥60 years in comparison to those aged 50-59 years (23% vs 8%, p = 0.001). Of all study patients, 44% took more than three drugs in addition to their ART, while 29% received no additional pharmacological interventions.

CONCLUSIONS: Comorbidities and risk factors for chronic diseases are very common in HIV-infected patients aged ≥50 years and increase with age, so they should be early considered in the clinical management of these patients. It is important to encourage healthy lifestyles to prevent comorbidities and to control risk factors. Concomitant treatments with ART should be carefully monitored to prevent drug interactions, adverse effects, and patient adherence failures.

PMID: 29486621 [Indexed for MEDLINE]

Curr Allergy Asthma Rep. 2018 Feb 22;18(3):15.

Impact of Particulate Air Pollution on Cardiovascular Health.

An Z, Jin Y, Li J, Li W, Wu W

PURPOSE OF REVIEW: Air pollution is established as an independent risk factor for cardiovascular diseases (CVDs). Ambient particulate matter (PM), a principal component of air pollutant, has been considered as a main culprit of the adverse effects of air pollution on human health.
RECENT FINDINGS: Extensive epidemiological and toxicological studies have demonstrated particulate air pollution is positively associated with the development of CVDs. Short-term PM exposure can trigger acute cardiovascular events while long-term exposure over years augments cardiovascular risk to an even greater extent and can reduce life expectancy by a few years. Inhalation of PM affects heart rate variability, blood pressure, vascular tone, blood coagulability, and the progression of atherosclerosis. The potential molecular mechanisms of PM-caused CVDs include direct toxicity to the cardiovascular system or indirect injury by inducing systemic inflammation and oxidative stress in circulation. This review mainly focuses on the acute and chronic effects of ambient PM exposure on the development of cardiovascular diseases and the possible mechanisms for PM-induced increases in cardiovascular morbidity and mortality. Additionally, we summarized some appropriate interventions to attenuate PM air pollution-induced cardiovascular adverse effects, which may promote great benefits to public health.

PMID: 29470659

Outcomes Cardiovasculares

Cardiol Rev. 2018 Mar 30. [Epub ahead of print]

Sodium-Glucose Cotransporter-2 Inhibition in Type 2 Diabetes Mellitus: A Review of Large-scale Cardiovascular Outcome Studies and Possible Mechanisms of Benefit.

Dalan R.

Cardiovascular (CV) disease remains the leading cause of morbidity and mortality in individuals with type 2 diabetes mellitus (T2DM). However, conventional anti-hyperglycemic medications seem to have minimal effect on lowering CV risk despite achieving excellent reductions in glycated hemoglobin A1c and associated reductions in microvascular risk. Sodium-glucose cotransporter 2 (SGLT2) inhibitors have emerged as noteworthy anti-hyperglycemic agents with concomitant CV and renal protection in T2DM patients. In this comprehensive review, we present the key CV findings from major large-scale outcome trials of SGLT2 inhibitors to date. We also review the mechanistic studies that might explain the CV benefits of SGLT2 inhibition in patients with T2DM.

PMID: 29608505

J Am Coll Cardiol. 2018 Mar 27;71(12):1379-1390.

Prevalent and Incident Heart Failure in Cardiovascular Outcome Trials of Patients With Type 2 Diabetes.

Greene SJ, Vaduganathan M, Khan MS, Bakris GL, Weir MR, Seltzer JH, Sattar N, McGuire DK, Januzzi JL, Stockbridge N, Butler J

Despite multiple examples of glucose-lowering therapies affecting heart failure (HF) risk, ascertainment of HF data in cardiovascular outcome trials of these medications has not been systematically characterized. In this review, large (n >1,000) published phase III and IV cardiovascular outcome trials evaluating glucose-lowering therapies through June 2017 were identified. Data were abstracted from publications, U.S. Food and Drug Administration advisory committee records, and U.S. Food and Drug Administration labeling documents. Overall, 21 trials including 152,737 patients were evaluated. Rates and definitions of baseline HF and incident HF were inconsistently provided. Baseline ejection fraction data were provided in 3 studies but not specific to patients with HF. No trial reported functional class, ejection fraction, or HF therapy at the time of incident HF diagnosis. HF hospitalization data were available in 15 trials, but only 2 included HF-related events within the primary composite endpoint. This systematic review highlights gaps in HF data capture within cardiovascular outcome trials of glucose-lowering therapies and outlines rationale and strategies for improving HF characterization.

PMCID: PMC5832063 [Available on 2019-03-27]
PMID: 29534825

Diabetes Res Clin Pract. 2018 Mar 6;139:107-113

Lower mortality and cardiovascular event rates in patients with Latent Autoimmune Diabetes In Adults (LADA) as compared with type 2 diabetes and insulin deficient diabetes: A cohort study of 4368 patients.

Wod M(1), Thomsen RW, Pedersen L, Yderstraede KB, Beck-Nielsen H, Højlund K

BACKGROUND: Latent Autoimmune Diabetes in Adults (LADA) is the second most common form of diabetes, but data on its clinical course and prognosis are scarce. We compared long-term risk of mortality and cardiovascular outcomes in patients with LADA, type 2 diabetes mellitus (T2D), and insulin deficient diabetes (IDD).

METHODS: We conducted a cohort study of 4368 adults with diabetes referred to the Department of Endocrinology, Odense University Hospital, Denmark, between 1997 and 2012. Data on comorbidity, cardiovascular outcomes and death were obtained from prospective medical databases. We compared adjusted hazard ratios (HRs) of mortality and cardiovascular outcomes for patients with LADA, T2D and IDD,
respectively.

RESULTS: We included 327 patients with LADA, 3539 with T2D and 502 with IDD. At diagnosis, patients with LADA were older (50 years (IQR 37-59)) than IDD patients (40 years (IQR 28-52)), but younger than patients with T2D (55 years (IQR 45-64)). During a median follow-up period of 6.6 years (IQR 3.4-9.4), patients with IDD had higher mortality than patients with LADA, age- and gender-adjusted HR 2.2 (95% CI, 1.5-3.2). T2D also conferred higher mortality than LADA, HR 1.4 (95% CI, 1.0-1.9). Compared with LADA patients, cardiovascular outcome rates were increased both with IDD, HR 1.2 (95% CI, 0.7-2.0) and T2D, HR 1.2 (95% CI, 0.8-1.8), with the strongest association observed for T2D vs. LADA and acute myocardial infarction HR 1.7 (95% CI, 0.8-3.5).

CONCLUSION: LADA seems to be associated with lower mortality and lower risk of cardiovascular events, compared with both T2D and IDD.

PMID: 29518492

Clin J Am Soc Nephrol. 2018 Apr 6;13(4):585-595.

Central Blood Pressure and Cardiovascular Outcomes in Chronic Kidney Disease.

Rahman M, Hsu JY, Desai N, Hsu CY, Anderson AH, Appel LJ, Chen J, Cohen DL, Drawz PE, He J, Qiang P, Ricardo AC, Steigerwalt S, Weir MR, Wright JT Jr, Zhang X, Townsend RR; CRIC Study Investigators.

BACKGROUND AND OBJECTIVES: Central BP measurements provide noninvasive measurement of aortic BP; our objectives were to examine the association of central and brachial BP measurements with risk of cardiovascular outcomes and mortality in patients with CKD and to determine the role of central BP measurement in conjunction with brachial BP in estimating cardiovascular risk.
DESIGN, SETTING, PARTICIPANTS, & MEASUREMENTS: In a prospective, longitudinal study (the Chronic Renal Insufficiency Cohort), central BP was measured in participants with CKD using the SphygmoCorPVx System. Cox proportional hazards models were used for analyses.
RESULTS: Mean age of the participants (n=2875) was 60 years old. After a median follow-up of 5.5 years, participants in the highest quartile of brachial systolic BP (≥138 mm Hg) were at higher risk for the composite cardiovascular outcome (hazard ratio, 1.59; 95% confidence interval, 1.17 to 2.17; c statistic, 0.76) but not all-cause mortality (hazard ratio, 1.28; 95% confidence interval, 0.90 to 1.80) compared with those in the lowest quartile. Participants in the highest quartile of central systolic BP were also at higher risk for the composite cardiovascular outcome (hazard ratio, 1.69; 95% confidence interval, 1.24 to 2.31; c statistic, 0.76) compared with participants in the lowest quartile.
CONCLUSIONS: We show that elevated brachial and central BP measurements are both associated with higher risk of cardiovascular disease outcomes in patients with CKD. Measurement of central BP does not improve the ability to predict cardiovascular disease outcomes or mortality in patients with CKD compared with brachial BP measurement.

PMID: 29475992

Clin Res Cardiol. 2018 Apr;107(4):271-280.

Cardio-oncology: conflicting priorities of anticancer treatment and cardiovascular outcome.

Tilemann LM, Heckmann MB, Katus HA, Lehmann LH, Müller OJ

BACKGROUND: This article about the emerging field of cardio-oncology highlights typical side effects of oncological therapies in the cardiovascular system, cardiovascular complications of malignancies itself, and potential preventive or therapeutic modalities.
METHODS: We performed a selective literature search in PubMed until September 2016.
RESULTS: Cardiovascular events in cancer patients can be frequently attributed to oncological therapies or to the underlying malignancy itself. Furthermore, many patients with cancer have pre-existing cardiovascular diseases that can be aggravated by the malignancy or its therapy. Cardiovascular abnormalities in oncological patients comprise a broad spectrum from alterations in electrophysiological, laboratory or imaging tests to the occurrence of thromboembolic, ischemic or rhythmological events and the impairment of left ventricular function or manifest heart failure.
DISCUSSION: A close interdisciplinary collaboration between oncologists and cardiologists/angiologists as well as an increased awareness of potential cardiovascular complications could improve clinical care of cancer patients and provides a basis for an improved understanding of underlying mechanisms of cardiovascular morbidity.

PMCID: PMC5869944
PMID: 29453595

Lancet Diabetes Endocrinol. 2018 Feb;6(2):105-113.

Cardiovascular outcomes with glucagon-like peptide-1 receptor agonists in patients with type 2 diabetes: a meta-analysis.

Bethel MA, Patel RA, Merrill P, Lokhnygina Y, Buse JB, Mentz RJ, Pagidipati NJ, Chan JC, Gustavson SM, Iqbal N, Maggioni AP, Öhman P, Poulter NR, Ramachandran A, Zinman B, Hernandez AF, Holman RR; EXSCEL Study Group.

Comment in

Lancet Diabetes Endocrinol. 2018 Feb;6(2):83-85.

BACKGROUND: Glucagon-like peptide-1 (GLP-1) receptor agonists are effective glucose-lowering drugs. Findings from cardiovascular outcome trials showed cardiovascular safety of GLP-1 receptor agonists, but results for cardiovascular efficacy were varied. We aimed to examine overall cardiovascular efficacy for lixisenatide, liraglutide, semaglutide, and extended-release exenatide.

METHODS: In this systematic review and meta-analysis, we analysed data from eligible trials that assessed the safety and efficacy of GLP-1 receptor agonists compared with placebo in adult patients (aged 18 years or older) with type 2 diabetes and had a primary outcome including, but not limited to, cardiovascular mortality, non-fatal myocardial infarction, and non-fatal stroke. We searched PubMed and MEDLINE without language restrictions up to Sept 18, 2017, for eligible trials. We did a meta-analysis of available trial data using a random-effects model to calculate overall hazard ratios (HRs) for cardiovascular efficacy outcomes and odds ratios for key safety outcomes.

FINDINGS: Of 12 articles identified in our search and screened for eligibility, four trials of cardiovascular outcomes of GLP-1 receptor agonists were

identified: ELIXA (lixisenatide), LEADER (liraglutide), SUSTAIN 6 (semaglutide), and EXSCEL (extended-release exenatide). Compared with placebo, GLP-1 receptor agonist treatment showed a significant 10% relative risk reduction in the three-point major adverse cardiovascular event primary outcome (cardiovascular mortality, non-fatal myocardial infarction, and non-fatal stroke; HR 0·90, 95% CI 0·82-0·99; p=0·033), a 13% RRR in cardiovascular mortality (0·87, 0·79-0·96; p=0·007), and a 12% relative risk reduction in all-cause mortality (0·88, 0·81-0·95; p=0·002), with low-to-moderate between-trial statistical heterogeneity. No significant effect of GLP-1 receptor agonists was identified on fatal and non-fatal myocardial infarction, fatal and non-fatal stroke, hospital admission for unstable angina, or hospital admission for heart failure. Overall, no significant differences were seen in severe hypoglycaemia, pancreatitis, pancreatic

cancer, or medullary thyroid cancer reported between GLP-1 receptor agonist treatment and placebo.

INTERPRETATION: Our findings show cardiovascular safety across all GLP-1 receptor agonist cardiovascular outcome trials and suggest that drugs in this class can reduce three-point major adverse cardiovascular events, cardiovascular mortality, and all-cause mortality risk, albeit to varying degrees for individual drugs, without significant safety concerns. GLP-1 receptor agonists have a favourable risk-benefit balance overall, which should allow the choice of drug to be individualised to each patient's needs.

FUNDING: Amylin P harmaceuticals (AstraZeneca).

PMID: 29221659

Diabetes Care. 2018 Feb;41(2):356-363.

How Does Empagliflozin Reduce Cardiovascular Mortality? Insights From a Mediation Analysis of the EMPA-REG OUTCOME Trial.

Inzucchi SE, Zinman B, Fitchett D, Wanner C, Ferrannini E, Schumacher M, Schmoor C, Ohneberg K, Johansen OE, George JT, Hantel S, Bluhmki E, Lachin JM

OBJECTIVE: In the BI 10773 (Empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME) trial involving 7,020 patients with type 2 diabetes and established cardiovascular (CV) disease, empagliflozin given in addition to standard of care reduced the risk of CV death by 38% versus placebo (hazard ratio [HR] 0.62 [95% CI 0.49, 0.77]). This exploratory mediation analysis assesses the extent to which treatment group differences in covariates during the trial contributed to CV death risk reduction with empagliflozin.

RESEARCH DESIGN AND METHODS: Effects of potential mediators, identified post hoc, on the HR for CV death with empagliflozin versus placebo were analyzed by Cox regression models, with treatment group adjusted for the baseline value of the variable and its change from baseline or updated mean (i.e., considering all prior values), each as a time-dependent covariate. HRs were compared with a model without adjustment for covariates. Multivariable analyses also were performed.

RESULTS: Changes in hematocrit and hemoglobin mediated 51.8% and 48.9%, respectively, of the effect of empagliflozin versus placebo on the risk of CV death on the basis of changes from baseline, with similar results in analyses on the basis of updated means. Smaller mediation effects (maximum 29.3%) were observed for uric acid, fasting plasma glucose, and HbA1c. In multivariable models, which incorporated effects of empagliflozin on hematocrit, fasting glucose, uric acid, and urine albumin:creatinine ratio, the combined changes from baseline provided 85.2% mediation, whereas updated mean analyses provided 94.6% mediation of the effect of empagliflozin on CV death.

CONCLUSIONS: In this exploratory analysis from the EMPA-REG OUTCOME trial, changes in markers of plasma volume were the most important mediators of the reduction in risk of CV death with empagliflozin versus placebo.

PMID: 29203583

J Hypertens. 2018 Feb;36(2):402-409.

Cardiovascular outcome in treatment-resistant hypertension: results from the Swedish Primary Care Cardiovascular Database (SPCCD).

Holmqvist L, Boström KB, Kahan T, Schiöler L, Hasselström J, Hjerpe P, Wettermark B, Manhem K

OBJECTIVE: To assess cardiovascular outcome in patients with treatment-resistant hypertension (TRH) compared with patients with nontreatment-resistant hypertension (HTN).
METHODS: Cohort study with data from 2006 to 2012 derived from the Swedish Primary Care Cardiovascular Database with hypertensive patients aged at least 30 years. TRH was defined as blood pressure at least 140/90mmHg despite medication adherence to three or more dispensed antihypertensive drug classes. Patients with cardiovascular comorbidity were excluded. The association between TRH and cardiovascular events with adjustment for important confounders was analyzed.
RESULTS: We included 4317 TRH patients and 32282 HTN patients. TRH patients (61% women) were older (70 vs. 66 years), had higher SBP (152 vs. 141mmHg) and more diabetes (30 vs. 20%) ($P<0.001$ for all) compared with HTN patients. Mean follow-up time was 4.3 years. In the adjusted analysis, TRH patients had an increased risk for total mortality [hazard ratio 1.12; 95% confidence interval (CI), 1.03-1.23], cardiovascular mortality (hazard ratio 1.20; 95% CI, 1.03-1.40) and incident heart failure (hazard ratio 1.34; 95% CI, 1.17-1.54) but not for incident stroke (hazard ratio 1.03; 95% CI, 0.90-1.19) or transitoric ischemic attack (hazard ratio 1.12; 95% CI, 0.86-1.46) compared with HTN patients.
CONCLUSION: Patients with TRH have a poor prognosis beyond blood pressure level, compared with hypertensive patients without TRH. In particular, the high risk for heart failure is of clinical importance and merits further investigation.

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Empagliflozin and Clinical Outcomes in Patients With Type 2 Diabetes Mellitus, Established Cardiovascular Disease, and Chronic Kidney Disease.

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BACKGROUND: Empagliflozin, a sodium-glucose cotransporter 2 inhibitor, reduced cardiovascular morbidity and mortality in patients with type 2 diabetes mellitus and established cardiovascular disease in the EMPA-REG OUTCOME trial (Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients). Urinary glucose excretion with empagliflozin decreases with declining renal function, resulting in less potency for glucose lowering in patients with kidney disease. We investigated the effects of empagliflozin on clinical outcomes in patients with type 2 diabetes mellitus, established cardiovascular disease, and chronic kidney disease.

METHODS: Patients with type 2 diabetes mellitus, established cardiovascular disease, and estimated glomerular filtration rate (eGFR) ≥30 mL·min-1·1.73 m-2 at screening were randomized to receive empagliflozin 10 mg, empagliflozin 25 mg, or placebo once daily in addition to standard of care. We analyzed cardiovascular death, hospitalization for heart failure, all-cause hospitalization, and all-cause mortality in patients with prevalent kidney disease (defined as eGFR <60 mL·min-1·1.73 m-2 and/or urine albumin-creatinine ratio >300 mg/g) at baseline. Additional analyses were performed in subgroups by baseline eGFR (<45, 45-<60, 60-<90, ≥90 mL·min-1·1.73 m-2) and baseline urine albumin-creatinine ratio (>300, 30-≤300, <30 mg/g).

RESULTS: Of 7020 patients treated, 2250 patients had prevalent kidney disease at baseline, of whom 67% had a diagnosis of type 2 diabetes mellitus for >10 years,
58% were receiving insulin, and 84% were taking angiotensin-converting enzyme inhibitors or angiotensin receptor blockers. In patients with prevalent kidney disease at baseline, empagliflozin reduced the risk of cardiovascular death by 29% compared with placebo (hazard ratio [HR], 0.71; 95% confidence interval [CI], 0.52-0.98), the risk of all-cause mortality by 24% (HR, 0.76; 95% CI, 0.59-0.99), the risk of hospitalization for heart failure by 39% (HR, 0.61; 95% CI, 0.42-0.87), and the risk of all-cause hospitalization by 19% (HR, 0.81; 95% CI, 0.72-0.92). Effects of empagliflozin on these outcomes were consistent across categories of eGFR and urine albumin-creatinine ratio at baseline and across the 2 doses studied. The adverse event profile of empagliflozin in patients with eGFR <60 mL·min-1·1.73 m-2 was consistent with the overall trial population.

CONCLUSIONS: Empagliflozin improved clinical outcomes and reduced mortality in vulnerable patients with type 2 diabetes mellitus, established cardiovascular disease, and chronic kidney disease.
CLINICAL TRIAL REGISTRATION: URL: https://www.clinicaltrials.gov. Unique identifier: NCT01131676.

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