

CROATIAN INTERNATIONAL PUBLICATIONS

by Ivan Boháček

ibohacek@hiim.hr



Giljaca V, Gurusamy KS, Takwoingi Y, Higgle D, Poropat G, Stimac D, Davidson BR. Endoscopic ultrasound versus magnetic resonance cholangiopancreatography for common bile duct stones. *Cochrane Database Syst Rev.* 2015;2:CD011549.

Department of Gastroenterology, Clinical Hospital Centre Rijeka, Rijeka, Croatia.

BACKGROUND: Endoscopic ultrasound (EUS) and magnetic resonance cholangiopancreatography (MRCP) are tests used in the diagnosis of common bile duct stones in patients suspected of having common bile duct stones prior to undergoing invasive treatment. There has been no systematic review of the accuracy of EUS and MRCP in the diagnosis of common bile duct stones using appropriate reference standards. **OBJECTIVES:** To determine and compare the accuracy of EUS and MRCP for the diagnosis of common bile duct stones. **SEARCH METHODS:** We searched MEDLINE, EMBASE, Science Citation Index Expanded, BIOSIS, and Clinicaltrials.gov until September 2012. We searched the references of included studies to identify further studies and of systematic reviews identified from various databases (Database of Abstracts of Reviews of Effects (DARE), Health Technology Assessment (HTA), Medion, and ARIF (Aggressive Research Intelligence Facility)). We did not restrict studies based on language or publication status, or whether data were collected prospectively or retrospectively. **SELECTION CRITERIA:** We included studies that provided the number of true positives, false positives, false negatives, and true negatives for EUS or MRCP. We only accepted studies that confirmed the presence of common bile duct stones by extraction of the stones (irrespective of whether this was done by surgical or endo-

scopic methods) for a positive test, and absence of common bile duct stones by surgical or endoscopic negative exploration of the common bile duct or symptom free follow-up for at least six months for a negative test, as the reference standard in people suspected of having common bile duct stones. We included participants with or without prior diagnosis of cholelithiasis; with or without symptoms and complications of common bile duct stones, with or without prior treatment for common bile duct stones; and before or after cholecystectomy. At least two authors independently screened abstracts and selected studies for inclusion. **DATA COLLECTION AND ANALYSIS:** Two authors independently collected the data from each study. We used the bivariate model to obtain pooled estimates of sensitivity and specificity. **MAIN RESULTS:** We included a total of 18 studies involving 2366 participants (976 participants with common bile duct stones and 1390 participants without common bile duct stones). Eleven studies evaluated EUS alone, and five studies evaluated MRCP alone. Two studies evaluated both tests. Most studies included patients who were suspected of having common bile duct stones based on abnormal liver function tests; abnormal transabdominal ultrasound; symptoms such as obstructive jaundice, cholangitis, or pancreatitis; or a combination of the above. The proportion of participants who had undergone cholecystectomy varied across studies. Not one of the studies was of high methodological quality. For EUS, the sensitivities ranged between 0.75 and 1.00 and the specificities ranged between 0.85 and 1.00. The summary sensitivity (95% confidence interval (CI)) and specificity (95% CI) of the 13 studies that evaluated EUS (1537 participants; 686 cases and 851 participants without common bile duct stones) were 0.95 (95% CI 0.91 to 0.97) and 0.97 (95% CI 0.94 to 0.99). For MRCP, the sensitivities ranged between 0.77 and 1.00

and the specificities ranged between 0.73 and 0.99. The summary sensitivity and specificity of the seven studies that evaluated MRCP (996 participants; 361 cases and 635 participants without common bile duct stones) were 0.93 (95% CI 0.87 to 0.96) and 0.96 (95% CI 0.90 to 0.98). There was no evidence of a difference in sensitivity or specificity between EUS and MRCP (P value = 0.5). From the included studies, at the median pre-test probability of common bile duct stones of 41% the post-test probabilities (with 95% CI) associated with positive and negative EUS test results were 0.96 (95% CI 0.92 to 0.98) and 0.03 (95% CI 0.02 to 0.06). At the same pre-test probability, the post-test probabilities associated with positive and negative MRCP test results were 0.94 (95% CI 0.87 to 0.97) and 0.05 (95% CI 0.03 to 0.09). **AUTHORS' CONCLUSIONS:** Both EUS and MRCP have high diagnostic accuracy for detection of common bile duct stones. People with positive EUS or MRCP should undergo endoscopic or surgical extraction of common bile duct stones and those with negative EUS or MRCP do not need further invasive tests. However, if the symptoms persist, further investigations will be indicated. The two tests are similar in terms of diagnostic accuracy and the choice of which test to use will be informed by availability and contra-indications to each test. However, it should be noted that the results are based on studies of poor methodological quality and so the results should be interpreted with caution. Further studies that are of high methodological quality are necessary to determine the diagnostic accuracy of EUS and MRCP for the diagnosis of common bile duct stones.

Brkovic E¹, Novak K², Puljak L³. Pain-to-hospital times, cardiovascular risk factors, and early intrahospital mortality in patients with acute myocardial infarction. *Ther Clin Risk Manag.* 2015;11:209-16.

¹Department of Psychiatry, University of Split School of Medicine, Split, Croatia; ²Department of Internal Medicine, Division of Cardiology, University of Split School of Medicine, Split, Croatia; ³Laboratory for Pain Research, University of Split School of Medicine, Split, Croatia.

BACKGROUND: The aim of the study was to analyze the most recent trends in myocardial infarction (MI) care, the number of patients treated for MI and their outcomes, cardiovascular disease risk factors, and pain-to-hospital times in MI patients. **SUBJECTS AND METHODS:** For 778 patients treated for acute MI at the Coronary Care Unit (CCU) of

University Hospital Split, Croatia the following data were acquired: outcome during hospitalization (survived, deceased), cardiovascular risk factors (hypertension, diabetes, dyslipidemia, previous MI, smoking), and pain-to-CCU time. **RESULTS:** Among 778 patients treated for acute MI, there were 291 (37%) women and 487 (63%) men. Forty-five patients (6%) died during hospitalization, mostly due to cardiogenic shock. An association was found between early intrahospital mortality and the following risk factors: age >70 years, female sex, previous MI, and smoking. Median pain-to-call time was 2 hours, and median time from the onset of pain to arrival into the CCU was 4 hours. There were 59 (7.6%) patients admitted to the CCU within recommended 90 minutes. Diabetic comorbidity was not associated with early death or with longer time from pain to emergency calls. **CONCLUSION:** Some of the risk factors associated with adverse outcomes in MI are modifiable. Prehospital delay of 4 hours observed in patients who suffered an MI is too long, and more effort should be devoted to investments in health care and education of the general public regarding chest pain symptoms.

Bralić Lang V¹, Bergman Marković B², Kranjčević K³. Family Physician Clinical Inertia in Glycemic Control among Patients with Type 2 Diabetes. *Med Sci Monit.* 2015;21:403-11.

¹Private Family Physician Office affiliated to University of Zagreb, School of Medicine, Zagreb, Croatia; ²Department of Family Medicine, University of Zagreb, School of Medicine, Zagreb, Croatia; ³General Practice Office, Zagreb-Zapad Health Care Center, Zagreb, Croatia.

BACKGROUND Many patients with diabetes do not achieve target values. One of the reasons for this is clinical inertia. The correct explanation of clinical inertia requires a conjunction of patient with physician and health care system factors. Our aim was to determine the rate of clinical inertia in treating diabetes in primary care and association of patient, physician, and health care setting factors with clinical inertia. **MATERIAL AND METHODS** This was a national, multicenter, observational, cross-sectional study in primary care in Croatia. Each family physician (FP) provided professional data and collected clinical data on 15-25 type 2 diabetes (T2DM) patients. Clinical inertia was defined as a consultation in which treatment change based on glycated hemoglobin (HbA1c) levels was indicated but did not occur. **RESULTS** A total of 449 FPs (response

rate 89.8%) collected data on 10275 patients. Mean clinical inertia per FP was 55.6% (SD \pm 26.17) of consultations. All of the FPs were clinically inert with some patients, and 9% of the FPs were clinically inert with all patients. The main factors associated with clinical inertia were: higher percentage of HbA1c, oral anti-diabetic drug initiated by diabetologist, increased postprandial glycemia and total cholesterol, physical inactivity of patient, and administration of drugs other than oral antidiabetics. CONCLUSIONS Clinical inertia in treating patients with T2DM is a serious problem. Patients with worse glycemic control and those whose therapy was initiated by a diabetologist experience more clinical inertia. More research on causes of clinical inertia in treating patients with T2DM should be conducted to help achieve more effective diabetes control.

Gradišer M¹, Dilber D², Cmrečnjak J³, Ostrički B⁴, Bilić-Ćurčić I⁵. Comparison of the Hospital Arrival Time and Differences in Pain Quality between Diabetic and Non-Diabetic STEMI Patients. *Int J Environ Res Public Health*. 2015;12(2):1387-96.

¹Department of Endocrinology and Diabetes, County Hospital Čakovec; ²Department of Cardiology, County Hospital Čakovec; ³Department of Cardiology, County Hospital Čakovec; ⁴Department of Cardiology, County Hospital Čakovec, Čakovec, Croatia; ⁵Clinical Department of Diabetes, Endocrinology and Metabolism Disorders, University Hospital Centre Osijek, Osijek, Croatia.

The aim of our study was to determine whether diabetic ST segment elevation myocardial infarction (STEMI) patients arrive in the emergency room (ER) later than non-diabetics, compare the differences in pain quality and quantity between those groups, and measure differences in the outcome after an index hospitalization. A total of 266 patients with first presentation of STEMI were included in our study during a period of two years, 62 with diabetes and 204 without diabetes type 2. Pain intensity and quality at admission were measured using a McGill short form questionnaire. Diabetic patients did not arrive significantly later than non-diabetic (χ^2 ; $p = 0.105$). Most diabetic patients described their pain as "slight" or "none" (χ^2 ; $p < 0.01$), while most non-diabetic patients graded their pain as "moderate" or "severe" (χ^2 ; $p < 0.01$). The quality of pain tended to be more distinct in non-diabetic patients, while diabetic patients reported mainly shortness of breath (χ^2 ; $p < 0.01$). Diabetic patients were more likely to suffer a

multi-vessel disease (χ^2 ; $p < 0.01$), especially in the late arrival group. Therefore, cautious evaluation of diabetic patients and adequate education of target population could improve overall survival while well-organized care like a primary PCI Network program could significantly reduce CV mortality.

Jelaković B¹, Vuković Lela I¹, Karanović S¹, Dika Ž¹, Kos J¹, Dickman K², Šekoranja M³, Poljičanin T⁴, Mišić M⁵, Premužić V¹, Abramović M⁶, Matijević V⁷, Miletić Medved M⁸, Cvitković A⁸, Edwards K⁹, Fuček M¹⁰, Leko N¹¹, Teskera T¹¹, Laganović M¹, Čvorišćec D¹⁰, Grollman AP². Chronic dietary exposure to aristolochic acid and kidney function in native farmers from a Croatian endemic area and Bosnian immigrants. *Clin J Am Soc Nephrol*. 2015;10(2):215-23.

¹Departments of Nephrology, Hypertension, Dialysis and Transplantation, School of Medicine, University of Zagreb, University Hospital Center Zagreb, Zagreb, Croatia; ²Department of Pharmacological Sciences, State University of New York at Stony Brook, Stony Brook, New York; ³Faculty for Natural Sciences, University of Zagreb, Zagreb, Croatia; ⁴National Institute for Public Health, Zagreb, Croatia; ⁵Cytology Unit, Slavonski Brod, Croatia; ⁶Outpatient Clinic Bebrina, Bebrina, Croatia; ⁷Outpatient Clinic Slavonski Kobaš, Croatia; ⁸Institute for Public Health County Brodsko-Posavska, Slavonski Brod, Croatia; ⁹Department of Epidemiology, Genetic Epidemiology Research Institute, School of Medicine, University of California, Irvine, Irvine, CA; ¹⁰Clinical Laboratory Diagnostics, School of Medicine, University of Zagreb, University Hospital Center Zagreb, Zagreb, Croatia; ¹¹General Hospital, "Josip Benčević", Department of Internal Medicine, Dialysis Unit.

BACKGROUND AND OBJECTIVES: Improvements in agricultural practices in Croatia have reduced exposure to consumption of aristolochic acid-contaminated flour and development of endemic (Balkan) nephropathy. Therefore, it was hypothesized that Bosnian immigrants who settled in an endemic area in Croatia 15-30 years ago would be at lower risk of developing endemic nephropathy because of reduced exposure to aristolochic acid. To test this hypothesis, past and present exposure to aristolochic acid, proximal tubule damage as a hallmark of endemic nephropathy, and prevalence of CKD in Bosnian immigrants were analyzed. **DESIGN, SETTING, PARTICIPANTS, & MEASUREMENTS:** In this cross-sectional observational study from 2005 to 2010,

2161 farmers were divided into groups: indigenous inhabitants from endemic nephropathy and nonendemic nephropathy villages and Bosnian immigrants; α -1 microglobulin-to-creatinine ratio >31.5 mg/g and eGFR <60 ml/min per 1.73 m² were considered to be abnormal. RESULTS: CKD and proximal tubule damage prevalence was significantly lower in Bosnian immigrants than inhabitants of endemic nephropathy villages (6.9% versus 16.6%; $P<0.001$; 1.3% versus 7.3%; $P=0.003$, respectively); 20 years ago, Bosnian immigrants observed fewer *Aristolochia clematitis* in cultivated fields (41.9% versus 67.8%) and fewer seeds among wheat seeds (6.1% versus 35.6%) and ate more purchased than homemade bread compared with Croatian farmers from endemic nephropathy villages (38.5% versus 14.8%, $P<0.001$). Both Croatian farmers and Bosnian immigrants observe significantly fewer *Aristolochia* plants growing in their fields compared with 15-30 years ago. Prior aristolochic acid exposure was associated with proximal tubule damage (odds ratio, 1.64; 95% confidence interval, 1.04 to 2.58; $P=0.02$), whereas present exposure was not (odds ratio, 1.31; 95% confidence interval, 0.75 to 2.30; $P=0.33$). Furthermore, immigrant status was an independent negative predictor of proximal tubule damage (odds ratio, 0.40; 95% confidence interval, 0.19 to 0.86; $P=0.02$). CONCLUSIONS: Bosnian immigrants and autochthonous Croats residing in endemic areas are exposed significantly less to ingestion of aristolochic acid than in the past. The prevalence of endemic nephropathy and its associated urothelial cancers is predicted to decrease over time.

Pilipović K¹, Župan Ž², Dolenc P¹, Mršić-Pelčić J¹, Župan G¹. A single dose of PPAR γ agonist pioglitazone reduces cortical oxidative damage and microglial reaction following lateral fluid percussion brain injury in rats. *Prog Neuropsychopharmacol Biol Psychiatry*. 2015;59C:8-20.

¹Department of Pharmacology, School of Medicine, University of Rijeka, Rijeka, Croatia; ²Department of Anesthesiology, Reanimatology and Intensive Care Medicine, School of Medicine, University of Rijeka, Rijeka, Croatia; Clinics of Anesthesiology and Intensive Care Medicine, Clinical Hospital Center Rijeka, Rijeka, Croatia.

Neuroprotective actions of the peroxisome proliferator-activated receptor- γ (PPAR γ) agonists have been observed in various animal models of the brain injuries. In this study we examined the effects of a single dose of pioglitazone on

oxidative and inflammatory parameters as well as on neurodegeneration and the edema formation in the rat parietal cortex following traumatic brain injury (TBI) induced by the lateral fluid percussion injury (LFPI) method. Pioglitazone was administered in a dose of 1mg/kg at 10min after the brain trauma. The animals of the control group were sham-operated and injected by vehicle. The rats were decapitated 24h after LFPI and their parietal cortices were analyzed by biochemical and histological methods. Cortical edema was evaluated in rats sacrificed 48h following TBI. Brain trauma caused statistically significant oxidative damage of lipids and proteins, an increase of glutathione peroxidase (GSH-Px) activity, the cyclooxygenase-2 (COX-2) overexpression, reactive astrocytosis, the microglia activation, neurodegeneration, and edema, but it did not influence the superoxide dismutase activity and the expressions of interleukin-1 beta, interleukin-6 and tumor necrosis factor-alpha in the rat parietal cortex. Pioglitazone significantly decreased the cortical lipid and protein oxidative damage, increased the GSH-Px activity and reduced microglial reaction. Although a certain degree of the TBI-induced COX-2 overexpression, neurodegeneration and edema decrease was detected in pioglitazone treated rats, it was not significant. In the injured animals, cortical reactive astrocytosis was unchanged by the tested PPAR γ agonist. These findings demonstrate that pioglitazone, administered only in a single dose, early following LFPI, reduced cortical oxidative damage, increased antioxidant defense and had limited anti-inflammatory effect, suggesting the need for further studies of this drug in the treatment of TBI.

Petrić Miše B, Boraska Jelavić T, Strikic A, Hrepić D, Tomić K, Hamm W, Tomić S, Prskalo T, Vrdoljak E. Long Follow-up of Patients With Locally Advanced Cervical Cancer Treated With Concomitant Chemobrachyradiotherapy With Cisplatin and Ifosfamide Followed by Consolidation Chemotherapy. *Int J Gynecol Cancer*. 2015;25(2):315-9.

Department of Oncology, University Hospital Split, Split, Croatia; Department of Oncology, University Hospital Mostar, Mostar, Bosnia and Herzegovina; Boehringer Ingelheim Pharma GmbH & Co KG, Ingelheim am Rhein, Germany; Department of Pathology, University Hospital Split, Split, Croatia.

OBJECTIVES: Locally advanced cervical cancer (LACC) is one of the leading health problems of the de-

veloping countries. We present long-term outcomes of treatment with a concomitant chemobrachyradiotherapy followed by consolidation chemotherapy regimen. **MATERIALS AND METHODS:** We treated 118 patients with LACC (International Federation of Gynecology and Obstetrics stages IB2-IVA) with external radiotherapy (50 Gy in 25 fractions) and concomitant chemobrachyradiotherapy (low-dose rate). Chemotherapy was applied during brachyradiotherapy (cisplatin on day 1 in combination with 24-hour infusion of ifosfamide and mesna uroprotection). Four cycles of consolidation chemotherapy were given starting 4 weeks after the second concomitant chemobrachyradiotherapy cycle. **RESULTS:** After median follow-up period of 99.3 months, we observed acceptable acute and late toxicity, local control rate of 97.5%, and an overall survival of 74.6% at 96 months. **CONCLUSIONS:** Chemobrachyradiotherapy regimen followed by consolidation chemotherapy described in this article is a valuable treatment option for LACC.

Kostović I, Sedmak G, Vukšić M, Judaš M. The relevance of human fetal subplate zone for developmental neuropathology of neuronal migration disorders and cortical dysplasia. CNS Neurosci Ther. 2015;21(2):74-82.

Croatian Institute for Brain Research, University of Zagreb School of Medicine, Zagreb, Croatia.

The human fetal cerebral cortex develops through a series of partially overlapping histogenetic events which occur in transient cellular compartments, such as the subplate zone. The subplate serves as waiting compartment for cortical afferent fibers, the major site of early synaptogenesis and neuronal differentiation and the hub of the transient fetal cortical circuitry. Thus, the subplate has an important but hitherto neglected role in the human fetal cortical connectome. The subplate is also an important compartment for radial and tangential migration of future cortical neurons. We review the diversity of subplate neuronal phenotypes and their involvement in cortical circuitry and discuss the complexity of late neuronal migration through the subplate as well as its potential relevance for pathogenesis of migration disorders and cortical dysplasia. While migratory neurons may become misplaced within the subplate, they can easily survive by being involved in early subplate circuitry; this can enhance their subsequent survival even if they have immature or abnormal physiological activity and misrouted connections and thus survive into adulthood. Thus, better understanding of subplate developmental history and various subsets of its neurons may help to elucidate certain types of neuronal disorders, including those accompanied by epilepsy.