EDITORIAL

Awaiting the first impact factor in 2012: summary of the most read articles in the *Polish Archives of Internal Medicine* 2009–2010

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I am pleased to announce that the first impact factor (IF) of the *Polish Archives of Internal Medicine* (*Pol Arch Med Wewn*), the official journal of the Polish Society of Internal Medicine, will be announced in June 2012. The predicted IF 2011 of the journal exceeds 1.0, and I hope that the actual value will be a nice surprise to all of you who support our efforts to make the *Pol Arch Med Wewn* the best clinical journal with the IF among the Polish clinical journals.

In recent years, the *Pol Arch Med Wewn*, which is devoted to internal medicine in the broadest sense, has markedly reinforced its position. An increasing number of readers from several countries gave the total number of 48,992 downloads from our open-access website (www.pamw.pl) in the first 11 months of the year 2011 (FIGURE).

ORIGINAL PAPERS The analysis of the most read articles yielded interesting results. At the end of 2011, the 4 most read original papers were identified, all of which were published in 2009. The papers addressed a wide spectrum of vital clinical issues with a marked predominance of topics related to cardiovascular disorders. A brief summary of the most read original articles is presented below.

How to reduce mortality in acute cardiogenic pulmonary edema? **Background and major findings** Acute cardiogenic pulmonary edema is associated with significant death rate. In contrast to meta-analyses published before 2008, the 3CPO (Three Interventions in Cardiogenic Pulmonary Oedema) randomized controlled trial (RCT) failed to demonstrate reduction in mortality associated with the use of noninvasive positive pressure ventilation (NPPV) in patients treated for acute cardiogenic pulmonary edema.

Potts et al.[1] performed a combined analysis of all clinical studies on this topic, including the 3CPO trial and addressed the reasons for a discrepancy in mortality estimates in those studies including differences in methodology and patient characteristics. The first set of data duplicated the RCTs selected in the Cochrane; the second set included all RCTs cited in any of the meta-analyses reviewed; and the third high-quality randomized trial set assessed data from those trials included in at least 4 of the 5 meta-analyses reviewed. Using the variable effect modes and Revman software, Potts et al.[1] observed a significantly decreased mortality risk ratio by 25% in patients treated with NPPV (RR 0.75; 95% CI: 0.61–0.92).

What does this paper add to current knowledge? The study provides strong evidence based on the available trials that NNPV leads to a significant mortality benefit from this intervention in patients with acute cardiogenic pulmonary edema, and such mode of therapy should be considered in all patients with this life-threatening condition.[1]

How to diagnose a first episode of deep-vein thrombosis? **Background and major findings** The GRADE working group developed framework for clinical practice guidelines (CPG) addressing diagnostic evaluation and significance of different test strategies for clinical outcomes and prognosis. Available CPG, such as those for diagnostic problems, are based on the current best evidence, rigorous assessment of the quality of evidence, and dichotomous classification of recommendations, i.e., strong vs. weak, reached by consensus. Despite controversy around the optimal diagnostic strategy in deep-vein thrombosis (DVT) and several clinical studies regarding this issue, it has

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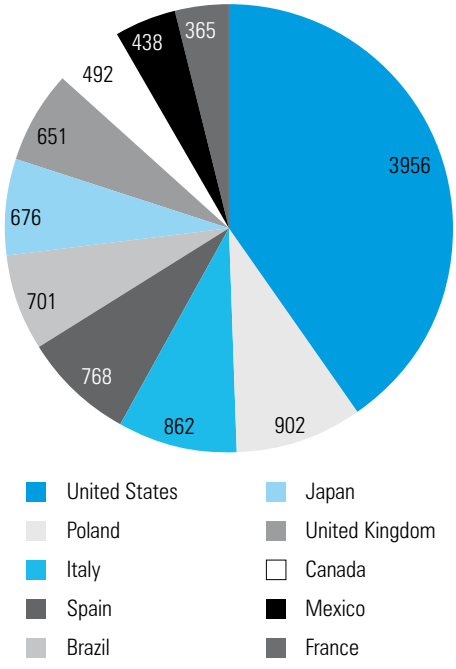
FIGURE Number of article downloads per country in the years 2009–2010



not been systematically addressed using modern methodology.

Jaeschke et al.[2] applied the GRADE approach to the diagnosis of DVT, which was their original concept to develop practical recommendations to crucial clinical questions based on existing CPG and systematic reviews. Importantly, Jaeschke et al.[2] provided practical recommendations not only for clinicians practicing in settings with access to both highly and moderately sensitive D-dimer tests, but also for those who are not able to determine circulating D-dimer levels. The recommendations focused on clinical relevance of venous ultrasound in association with D-dimer measurement depending on the initial probability of DVT.

In individuals with suspicion of DVT the 4 basic rules should be followed to guide diagnostic process:

1 When D-dimer measurement is unavailable, clinicians should rely on the results of venous ultrasound.

2 When D-dimer measurement is available, clinicians should determine D-dimer by one of the highly sensitive tests in all patients with low or moderate probability of DVT preferentially assessed by the Wells rule.

3 Patients with low pretest probability and a negative D-dimer should be followed without further testing.

4 Patients with high pretest probability should be subjected to a compression ultrasound without D-dimer testing.[2]

What does this paper add to current knowledge? The recommendations developed by Jaeschke et al.[2] were the first to summarize the current knowledge on diagnostic process in DVT and may have major impact on everyday practice in high- and low-income countries.

How does Turner syndrome affect the cardiovascular system? **Background and major findings** Turner syndrome is associated with a 3-fold higher mortality, mainly for cardiovascular disease, and this risk could be at least in part dependent on karyotype. However, this concept is controversial. Poprawski et al.[3] studied 34 women with Turner syndrome from 1 center using the findings of clinical examination, echocardiography, and electrocardiograms. The patients were categorized into 3 groups based on the karyotype, i.e., 1) monosomy X (45,X), 2) mosaicism, and 3) structural X chromosome aberrations. Congenital cardiovascular malformations were detected in 21% of the patients with Turner syndrome. Half of the patients had valvular heart disease, including aortic valve diseases in 24% and mitral valve defects in 21% of the patients. Patients with mosaicism were more often overweight, tended to suffer more commonly from arterial hypertension, and had thicker interventricular septum with larger left ventricular mass on echocardiography than those with monosomy X.[3]

What does this paper add to current knowledge? Congenital cardiovascular malformations are more common in women with Turner syndrome; however, no major impact of various karyotypes was observed. Only slight differences were noted between patients with mosaicism and those with monosomy X. Women from the former group tended to have higher body mass, blood pressure, and evidence of left ventricular hypertrophy.[3]

What causes severe iatrogenic hyperkalemia in cardiovascular patients? **Background and major findings** Medications commonly used in patients with cardiovascular disease, particularly inhibitors of renin-angiotensin-aldosterone (RAA) axis, affect potassium homeostasis in the kidneys or the gastrointestinal tract. A typical electrolyte disturbance induced by those medications is hyperkalemia, which may lead to muscle damage, neurological abnormalities, cardiovascular disorders, and finally death. Proportions of patients who developed iatrogenic hyperkalemia varies among studies and tends to be relatively high despite a number of protective strategies.

Wożakowska-Kapłon et al.[4] assessed the incidence and clinical manifestations of moderate and severe iatrogenic hyperkalemia in 26 patients hospitalized for cardiovascular disease in the years 2005–2006 (0.46% of all patients treated at that time at the ward), who on admission to hospital had blood potassium >6.0 mmol/l. Prior to admission, all patients were treated in outpatient clinics with angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers, spironolactone, amiloride, triamterene, β-blockers, or potassium supplements administered in monotherapy or in combination. Most of the hyperkaliemic patients were elderly women and had increased renal function parameters. The most common diseases observed in

that group were arterial hypertension (n = 21, 81%) and diabetes (n = 10, 38%). Severe bradyarrhythmia and complete atrioventricular block requiring temporary pacing were observed in 21 patients (81%). Mortality rate in that group was as high as 10% (3 of 26 patients).[4]

What does this paper add to current knowledge? The study provides additional evidence that administration of several medications in elderly outpatients, including inhibitors of the RAA system, is still associated with a significant risk of hyperkalemia burdened with significant mortality. Therefore, regular laboratory tests, including serum creatinine and potassium, are highly recommended both prior to and during treatment with drugs that may cause severe hyperkalemia.[4]

REVIEW PAPERS As in the majority of clinical medicine journals, review papers represent the most read articles in the *Pol Arch Int Med*. Problems addressed by authors along with their personal commentaries on diagnostic and therapeutic strategies, intertwined with rock hard evidence derived from clinical trials, have also been the most cited papers of our journal. The most interesting topics according to our readership that were addressed by the authors of the top 5 review papers are presented below.

Is combination of clopidogrel and proton-pump inhibitors safe? The risk of a significant clinical interaction between clopidogrel and proton-pump inhibitors (PPIs) has generated great controversy in recent years. Given a large proportion of patients receiving both medications, some experts recommended withdrawal of PPIs in high-risk subjects on clopidogrel therapy to reduce the probability of nonresponsiveness to clopidogrel and thrombotic complications, in particular in-stent thrombosis. Based on the data available until mid-2009, mostly the results of observational studies, a group of Polish experts summarized arguments to support the view that clopidogrel may interact with PPIs, given the fact that metabolism of both drugs is via similar cytochrome P450 isoenzymes. Several laboratory studies have shown that PPIs may attenuate platelet inhibition by clopidogrel. Clinical relevance of these findings remains to be clarified. In 2009, Polish experts recommended the continued use of PPIs in patients on dual platelet therapy who have clinical indications. It was highlighted that as both drugs have short half-lives, a 12-hour interval between intake of clopidogrel and of PPIs (e.g., in the morning and evening) may limit the risk of such potentially dangerous interaction.[5]

What is the best first-line pharmacological therapy for depression? Major depressive disorders are common in the general population resulting in a high risk of suicide worldwide. Several classes of safer antidepressants have been developed and marketed, which improved treatment outcomes and increased the number of depressed individuals treated for depression by their primary care physicians. Koenig et al.[6] reviewed practical aspects of the use of antidepressants that represent the first-line therapy for major depressive disorder (MDD), namely, the selective serotonin reuptake inhibitors, the serotonin and norepinephrine reuptake inhibitors, and the norepinephrine-dopamine reuptake inhibitor. All 3 classes of antidepressants offer superior tolerability and safety over older medications such as the tricyclic antidepressants. However, universally effective pharmacologic therapy for MDD has not been established yet. Special attention should be paid to assessment of medication response and management of potential side effects.[6]

How to use opioids on a long-term basis in patients with chronic noncancer pain? There is general consensus that safe and effective chronic opioid therapy for chronic noncancer pain is challenging, and particular emphasis should be placed on risks associated with opioid abuse, addiction, and diversion. The key practical recommendations from a systematic review have been prepared by the expert panel for the American Pain Society and the American Academy of Pain Medicine and presented by Chow.[7] The recommendations addressed patient selection and risk stratification, informed consent and opioid management plans, initiation and titration of chronic opioid therapy, use of methadone, monitoring of patients, use of opioids in high-risk patients, assessment of aberrant drug-related behaviors, dose escalations and high-dose opioid therapy, opioid rotation, indications for discontinuation of therapy, prevention and management of opioid-related adverse effects, as well as driving and work safety.[7]

How to optimally manage patients with arterial hypertension? Growing evidence indicates that treatment decision in hypertensive patients should be based on the overall cardiovascular risk, in which arterial blood pressure (BP) is only one of several components. BP lowering should be combined with effective lifestyle changes. Chalmers and Arima[8] showed in their comprehensive review, based on data from meta-analyses published by the Blood Pressure Lowering Treatment Trialists' Collaboration, that effectiveness of various classes of antihypertensive agents is almost similar across different age groups. The current guidelines now "recommend a focus on building effective drug combinations rather than arguing about which drug to use, and they approve initiation of treatment with combinations in high risk groups".[8] Nevertheless, the authors stressed out that there are some differences in the efficacy of individual drug classes in decreasing the risk of coronary artery disease and its complications, stroke, and heart failure. The relevance of the differences appears reduced given the paucity of comparative studies that evaluated outcomes while using various drug combinations.

Chalmers and Arima[8] proposed their own preferred combinations, namely 1) ACEIs and diuretics, which are the first-line option for white

patients, and 2) angiotensin receptor blockers (ARBs) in combination with diuretics in case of ACEI intolerance. Of note, black hypertensive patients are particularly likely to benefit from the combination of ACEIs and calcium channel blockers or that of calcium channel blockers and diuretics in individuals with isolated systolic hypertension. The authors discouraged from using the following combinations in patients with uncomplicated hypertension: 1) ACEIs and β-blockers and 2) ACEIs and ARBs.[8] The ability to skillfully combine antihypertensive drugs is the basis for effective antihypertensive therapy based on the current guidelines.

Could cyclooxygenase-2 selective inhibitors be used in subjects with cardiovascular disorders? It is well known that administration of nonsteroidal anti-inflammatory drugs (NSAIDs) is associated with gastrointestinal and other adverse effects. Selective cyclooxygenase-2 (COX-2) inhibitors, e.g., rofexocib and celexocib, which significantly lower the risk of upper gastrointestinal ulcers, bleeding, and perforations, have been demonstrated to increase the rate of thrombotic vascular events, including myocardial infarction. Despite the paucity of long-term data on cardiovascular risk associated with nonselective NSAIDs published until 2009, it appears that both selective COX-2 inhibitors and traditional NSAIDs may increase the risk of cardiovascular events. This resulted in somewhat inconsistent recommendations to apply these drugs in patients at high cardiovascular risk. The review paper by Głuszko and Bielińska[9] summarized the 2009 recommendations with special focus on the risk of serious adverse events associated with the use of NSAIDs.[9]

How to diagnose and treat patients with fibromyalgia? Since the term "fibromyalgia" was introduced by Smythe in 1976 to describe the generalized pain and tenderness on palpation at specific points, much progress has been made to elucidate the pathogenesis of this disease and improve treatment outcomes. However, a number of riddles need to be solved. Podolecki et al.[10] presented the update on the current knowledge on the etiology, pathophysiology, and management of subjects diagnosed with fibromyalgia, which is a quite mysterious and common disorder. Recent findings increased our understanding of fibryomyalgia by showing the role of altered neuronal activity in the central nervous system, abnormal metabolism of biogenic amines, and immune disorders. Given the fact that most signs of the disease are subjective, differentiation between fibromyalgia and both chronic fatigue syndrome and psychosomatic diseases is a difficult diagnostic challenge. Treatment options for patients diagnosed with fibromyalgia involve antidepressants, psychotherapy, and locally used agents to reduce pain. Since fibromyalgia is increasingly common in Western countries, implementation of current recommendations regarding diagnostic process and appropriate treatment is of particular importance.[10]

Publications from 2010 have also been read and increasingly cited. These papers arouse much interest among readers, which will help keep our IF at the same level in subsequent years. The most read articles from the *Pol Arch Med Wewn* are discussed below.

How to assess the risk in syncope and to manage the affected individuals in 2010? The European Society of Cardiology has recently revised its guidelines on the diagnosis and management of syncope. Sutton et al.[11] provided a synopsis of their recommendations. From the practical point of view, the criteria which require prompt hospitalization or intensive evaluation of the affected patients are of key importance. The features comprised the following: diagnosis of severe structural or coronary artery disease (heart failure, low left ventricular ejection fraction, or previous myocardial infarction); clinical or electrocardiographic features suggestive of arrhythmia as a cause of syncope (e.g., syncope during exertion, palpitations at the time of syncope, bifascicular block, sinus bradycardia, pre-excited QRS, prolonged or short QT interval, the Brugada pattern of abnormalities).

What is the current role of glycated hemoglobulin in diagnosing diabetes? The International Expert Committee recommends that the diagnosis of diabetes be made if hemoglobin A_{1c} (HbA_{1c}) level is greater than 6.5% and confirmed with a repeat HbA_{1c} test. Methodological differences in blood HbA_{1c} testing may confound data interpretation and the results could not be concordant. Fasting plasma glucose, 2-hour postglucose-load plasma glucose, and oral glucose tolerance tests should be preformed to establish or preclude diabetes only if one of the 3 situations is present, namely, HbA_{1c} testing is unavailable, patient factors that preclude its interpretation, and during pregnancy. Advantages of HbA_{1c} testing include greater clinical convenience, preanalytic stability, and assay standardization. There are factors that may influence HbA_{1c} test results leading to systematically increased or reduced values relative to the actual glycemia. It should be highlighted that HbA_{1c} in combination with plasma glucose determination is an optimal diagnostic approach for the diagnosis of diabetes. Of note, a diagnostic cut-off point of HbA_{1c} at 6.5% is associated with a decreased number of type 2 diabetic patients, in particular subjects with fasting hyperglycemia and people with impaired glucose tolerance. Combination of HbA_{1c} testing and plasma glucose measurements has been proposed to minimize systematic bias inherent in HbA_{1c} testing alone.[12]

What is the position of antileukotriene drugs in asthma treatment? Antileukotriene medications used in the treatment of asthma and allergic rhinitis are recommended in the recent GINA (Global

Initiative for Asthma) guidelines, the PRACTALL (Practicing Allergology) report on asthma treatment in children, and ARIA (Allergic Rhinitis and its Impact on Asthma) guidelines. Specific leukotriene receptor antagonists (montelukast, zafirlukast, pranlukast) and leukotriene biosynthesis inhibitors (zileuton) are listed as drugs controlling the course of the disease that could be an alternative to low-dose inhaled glucocorticosteroids in the second level of asthma severity and complement the use of inhaled and/or oral glucocorticosteroids, in the third level of asthma severity or even in more severe cases. Interestingly, antileukotriene drugs have been shown to be useful in patients with isolated allergic rhinitis, chronic cough in the course of asthma, as a sole symptom of the disease, and as therapy for episodes of wheezing caused by viral infections.[13] It is likely that in the future, this group of drugs will be used in allergic disorders other than asthma.

How to manage nonvariceal upper gastrointestinal bleeding? Several new recommendations regarding the management of patients with nonvariceal upper gastrointestinal bleeding have been introduced. Of vital clinical importance are initial adequate resuscitation and risk stratification using validated scales. The use of intravenous erythromycin is recommended to improve visualization when likely to find blood in the stomach. It has been stressed out that administration of PPI prior to endoscopy has no effect on the outcomes. In patients treated with anticoagulants, normalization of coagulation is needed; however, any delay in performing early endoscopy (within 24 h) is harmful and should be avoided. The detection of high-risk endoscopic stigmata should prompt the use of epinephrine injection combined with another modality such as clips, thermal or sclerosant injection, which are also efficacious alone. Adherent clots can be treated with high-dose intravenous PPI infusion alone or following endoscopic hemostasis. A second-look endoscopy is recommended only in selected patients following endoscopic hemostasis. Acetylsalicylic acid (ASA) can soon be restarted acutely after bleeding. However, concomitant administration of PPI on a long-term basis is necessary in patients with a history of previous bleeding while treated with NSAIDs if still needed. Despite the fact that nonvariceal upper gastrointestinal bleeding is life-threatening, implementation and dissemination of recent recommendations is suboptimal.[14]

How to diagnose and treat bone disorders in chronic kidney disease? KIDNEY DISEASE: Improving Global Outcomes (KDIGO), a nonprofit foundation to improve the care and outcomes of kidney disease patients worldwide, aims at coordination of initiatives to develop and implement clinical practice guidelines. Recommendations how to manage bone disorders in patients with chronic kidney disease were published in August 2009. The major issues addressed in these guidelines involve the diagnosis of biochemical, bone, and vascular abnormalities, therapeutic approaches to lower high serum phosphorus and to normalize serum calcium, and in dialysis patients to maintain parathormone levels in the range of 2 to 9 times exceeding the normal limit. Due to the lack of reliable comparative studies on the use of different phosphate binders, vitamin D analogs, and calcimimetics in this clinical setting, it is unclear whether these drugs can lower mortality. Therefore, the KDIGO experts do not make any specific recommendation in this regard. The treatment of osteoporosis using bisphosphonates and evaluation and treatment of bone disease developing after the kidney transplant are recommended.[15]

In conlusion, I would like to ask and encourage all readers to cite the papers published in the *Pol Arch Med Wewn* to increase the visibility of Polish internal medicine and the Polish Society of Internal Medicine worldwide at least in part by improving the IF 2012 of its major journal. We all strongly believe that further improvement of the quality of the journal is our common task for the sake of internal medicine, which struggles for a decent place in the Polish health care system.

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