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REVIEW UPDATE

Research update for articles published in EJCI in 2016

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1 | ENERGY METABOLISM, LIVER AND KIDNEY FUNCTION IN ADOLESCENT MARATHON RUNNERS[1] (MARTIN BURTSCHER)

Following the publication of our study,[1] no biochemical data derived from adolescent marathon runners have been made available. However, there are two potentially relevant investigations including adult runners. Shin et al[2] demonstrated different effects depending on the running distance, that is marathon, 100 and 308 km. Hepatic function was more impaired after completing 308 km (low intensity, long duration) compared to marathon or 100 km, but renal dysfunction was more pronounced after marathon and especially after 100 km (higher intensity and shorter duration). Another study reported elevated creatinine levels immediately post-marathon, being equivalent to acute kidney injury (AKI) stages 1 and 2 in 82% of runners.[3] However, values returned to baseline 24 hours postmarathon as shown in adolescent runners.[1] Whether the high AKI incidence represents an age effect or is a consequence of repeated marathon running or remains clinically irrelevant has to be proved.

2 | OUTCOME OF CONSERVATIVE MANAGEMENT VS ASSIST DEVICE IMPLANTATION IN PATIENTS WITH ADVANCED REFRACTORY HEART FAILURE[4] (CHRISTOPHER ADLBRECHT AND MARTIN HUELSMANN)

We reported favourable survival in advanced heart failure (HF) patients treated medically, compared to ventricular assist device (VAD) implantation.[4] Since then, the ENDURANCE trial comparing axial-flow to a centrifugal-flow device[5] and MOMENTUM 3 comparing a centrifugal-flow with an axial-flow VAD were published.[6] Neither study compared VAD to conservative medical therapy. The evolvement of HF-specific medical therapy and cardiac resynchronization since REMATCH has led to a dramatic reduction in mortality. The ROADMAP study in NYHA IIIb/IV ambulatory HF patients demonstrated no difference in the intention to treat analysis in 2-year survival.[7] Another observational study reported similar waitlist mortality among patients bridged with VAD or IV inotropes.[8] In summary, patient selection is still challenging, the perfect device is not available yet, the role of concomitant medical therapy is unclear, and data on survival compared to contemporary conservative medical management are not available. New data therefore reinforce our conclusion made.

3 | FUNCTIONAL CHARACTERIZATION OF THE HGRAT556I CAUSING CHROUSOS SYNDROME[9] (NICOLAS C. NICOLAIDES AND EVANGELIA CHARMANDARI)

Several genetic defects in the *NR3C1* gene encoding the human glucocorticoid receptor have been associated with primary generalized glucocorticoid resistance or Chrousos syndrome. This is a rare endocrinologic condition characterized by hypercortisolism without any clinical manifestations of Cushing syndrome. A recent French study found for the first time that the prevalence of *NR3C1* mutations in bilateral adrenal hyperplasia was 5%, indicating that many cases of Chrousos syndrome presenting only with adrenal hyperplasia may be underdiagnosed.[10] A second interesting study

described a new case of Chrousos syndrome who presented with infertility, hypercortisolism and hyperandrogenism.[11] The patient harboured a point *NR3C1* mutation (c.2141G→A), which resulted in an Arg714Gln substitution. Interestingly, the same genetic defect was found in her asymptomatic sister,[11] as well as in a child with a severe clinical phenotype.[12] The new generation sequencing technologies will undoubtedly unravel new players in the pathogenesis of Chrousos syndrome.

4 | ASSOCIATION OF MYELOPEROXIDASE LEVELS WITH CARDIOMETABOLIC FACTORS AND RENAL FUNCTION IN PREPUBERTAL CHILDREN[13] (LIANE CORREIA-COSTA AND TERESA SOUSA)

We reported that higher myeloperoxidase concentrations were associated with greater cardiometabolic risk and higher glomerular filtration rate (GFR) in prepubertal overweight/obese children.[13] We further showed that myeloperoxidase correlated positively with isoprostanes which, in turn, were positively correlated with insulin resistance and triglycerides in the same children.[14] Noteworthy, in a recent study involving 930 prepubertal children, myeloperoxidase was shown to be increased in children presenting cardiometabolic derangements and to contribute to this metabolically unhealthy status, in adjusted regression models.[15] No new evidence was found regarding myeloperoxidase association with nondipping or pulse wave velocity. Myeloperoxidase association with GFR was not observed in a study involving older children with obesity and type 1 diabetes.[16] However, this was not analysed separately for obese children and GFR was calculated with Bouvet formula,[16] which is limited by the use of Jaffe method assessed creatinine and appears to underestimate GFR values.[17]

5 | GENDER-RELATED DIFFERENCES IN ELDERLY PATIENTS WITH MYOCARDIAL INFARCTION IN A EUROPEAN CENTRE[18] (PATRICK SULZGRUBER AND ALEXANDER NIESSNER)

Women presenting with acute myocardial infarction (AMI) are still managed in a much less aggressive and invasive way than men.[18,19] However, women who received any reperfusion strategy were found to have an even lower risk of death compared to male individuals.[18] Of note, a recent investigation observed that female AMI patients were less likely to receive optimal medical therapy and care during the hospitalization of the acute event than their male counterparts.[19] Similarly, the results of a pooled analysis of patients undergoing coronary intervention revealed that women had a significantly higher 1-year morality rate compared to men that could not be explained by baseline characteristics, infarction size and postinfarction cardiac functioning—rather triggered by poor post-AMI patient care.[20] Those results foster the clinical importance of the observed gender gap, concluding that women may have better outcomes if treated with the same level of both invasive management and post-AMI care as their male counterparts.[21]

6 | HYPERTENSION SUBTYPES MODIFY METABOLIC RESPONSE TO THIAZIDE DIURETICS[22] (JAW-WEN CHEN)

We have previously shown that in a Taiwanese cohort, treatment with 50 mg of hydrochlorothiazide daily for 2 weeks improved serum cholesterol and fasting blood sugar levels suggesting a favourable metabolic response mainly for patients with diastolic hypertension.[22] In a recent study of 50 Japanese patients with type 2 diabetes whose blood pressure failed to reach target levels with 8 mg of candesartan alone, blood pressure improved similarly with the add-on of eplerenone or hydrochlorothiazide over 12 months, body mass index, waist circumference and low density lipoprotein-cholesterol were decreased in the former and glycohemoglobin was elevated in the later group. Such effects were not related to the presence of systolic or diastolic hypertension.[23] Taken together, the metabolic effects of hydrochlorothiazide treatment may be related to the baseline metabolic status, treatment duration and the type of hypertension. The optimal use of hydrochlorothiazide should be further classified in Asian population.

7 | SOLUBLE GALECTIN-3 IS ASSOCIATED WITH PREMATURE MYOCARDIAL INFARCTION[24] (MAX-PAUL WINTER AND GEORG GOLIASCH)

To date, no new evidence on galectin-3 has accumulated in patients with premature acute myocardial infarction. However, recent research could show that galectin-3 is a strong and independent predictor of left ventricular (LV) remodelling in patients after anterior-wall myocardial infarction treated by primary percutaneous coronary intervention. Irrespective of LV ejection fraction and infarct size, galectin-3 measured during hospitalization predicted adverse LV remodelling defined as an increase of at least 15% of LV end-diastolic volume after

6 months in patients with anterior STEMI.[25] Furthermore in a translational porcine model of coronary microembolism-induced postischaemic cardiac remodelling, galectin-3 could be localized in areas of tissue damage and myocardial fibrosis, with proportionate increase in the respective serum galectin-3 expression levels.[26] Another translational murine model could identify galectin-3 as a mediator of postischaemic, macrophage mediated myocardial inflammation and suggested it may represent a potential target for therapeutic inhibition.[27]

8 | NATIONAL CURVES OF FOETAL GROWTH IN SINGLETON FOETUSES OF GREEK ORIGIN[28] (ALEXANDROS SOTIRIADIS AND MAKARIOS ELEFTHERIADES)

Foetal growth assessment and monitoring are an essential component of prenatal care with postnatal impact. We have constructed reference ranges for foetal biometric parameters in Greek foetuses and compared them with previously published models. We concluded that using charts from other populations (including INTERGROWTH-21st) may be unrepresentative of local populations and lead to misclassification of foetal growth status. This is in accordance with findings from other studies[29,30] that the use of the INTERGROWTH-21st standard underestimates the proportion of SGA live births and SGA infants at risk of perinatal mortality and morbidity. Furthermore, both The Eunice Kennedy Shriver National Institute of Child Health and Human Development A study[31] that was designed to assess whether specific racial/ethnic-specific foetal growth standards were needed and the PRB/NICHD Detroit study[32] concluded that there is highly statistically significant racial/ethnic differences in foetal growth resulting in the publication of racial/ethnic-specific derived standards supporting our findings about the need of customized rather than multinational formulas.

9 | ACTIVATION OF EXTRACELLULAR SIGNAL-RELATED KINASE IN ABDOMINAL AORTIC ANEURYSM[33] (MENNO EVERT GROENEVELD AND KAK KHEE YEUNG)

Extracellular signal-related kinase (ERK) activation is associated with aortic aneurysm (AA) development and is enhanced in nonruptured AA.[33] ERK is a signalling protein responsible for aortic wall maintenance by vascular smooth muscle cell (VSMC) proliferation and migration. When ERK activation is inhibited, it can reduce the inflammatory response in VSMC and eventually reduces AAA development.[34,35] When ERK activation was blocked in TGBR1 deficient mice, aneurysmal degeneration was prevented.[36] Increased ERK activation in rats leads to enhanced aortic VSMC contractility resulting in hypertension and eventually cardiovascular disease like AAA.[37] However, in our unpublished pilot-studies, we measured impaired VSMC contractility in sporadic AAA and demonstrated a correlation between AAA growth rate in vivo vs contractility in vitro. The correlation of VSMC contraction with ERK-pathway is now still under investigation. The above-mentioned findings suggest that ERK has a deteriorating effect, rather than a protective role in AAA development.

10 | HIGHER HYDROCORTISONE DOSE INCREASES BILIRUBIN IN HYPOPITUITARY PATIENTS—RESULTS FROM AN RCT[38] (ROBIN P. F. DULLAART AND ANDRÉ P. VAN BEEK)

The cardioprotective properties of bilirubin are increasingly recognized.[39] In line, low serum bilirubin levels were observed to be associated with incident hypertension.[40] The heme oxygenase (HO) system is pivotal for bilirubin generation, and the expression of HO-2 isoenzyme is upregulated by glucocorticoids. Our randomized trial among 47 hypopituitary patients showed that doubling of the hydrocortisone replacement dose elicited a significant 10% increase in serum total bilirubin.[38] In keeping with a bilirubin raising effect of glucocorticoids, a study of 60 children with minimal change nephropathy showed that prednisone in a maximal daily dose of 60 mg, either alone or in combination with fluvastatin, increased serum bilirubin.[41] More recently, high dose prednisone treatment was found to increase serum bilirubin in 50 patients with active-phase Takayasu arteritis.[42] So, although available evidence is still limited, evidence is mounting that glucocorticoids are able to elevate circulating bilirubin.

11 | ALISKIREN DIRECTLY IMPROVES ENDOTHELIAL PROGENITOR CELL FUNCTION FROM TYPE II DIABETIC PATIENTS[43] (TING-TING CHANG AND JAW-WEN CHEN)

Our previous studies indicated that aliskiren, a direct renin inhibitor, could directly improve the function of endothelial progenitor cells from patients with type 2 diabetes[43] and improve neovasculogenesis for hindlimb ischaemia in diabetic animals.[44] The beneficial effects of aliskiren might be related to the upregulation on vascular endothelial growth

factor/stromal cell-derived factor-1α (VEGF/SDF-1α) singles via the activation of (pro)renin receptor-related pathway.[43] Interestingly, aliskiren could also reduce the expression of (pro)renin receptor in glomeruli, renal tubules and renal cortical vessels of diabetic animals but not in human renal mesangial cells. Accordingly, aliskiren might act differentially on different cells in different models. In line with the above hypothesis, recent findings suggested that aliskiren could suppress angiogenesis in a L-NAME-induced hypertension rat model[45] and decrease oxidative stress as well as angiogenic markers in angiotensin II treated retinal pigment epithelium cells.[46] Further studies are needed to clarify the universal mechanisms of aliskiren.

12 | MITOCHONDRIAL BIOENERGETICS AND POSTHEPATECTOMY LIVER DYSFUNCTION[47] (HENRIQUE ALEXANDRINO AND CARLOS PALMEIRA)

Liver regeneration is highly energy-dependent.[48,49] Our group has previously demonstrated that in humans, intraoperative deterioration in mitochondrial oxidative phosphorylation can be caused by prolonged hepatic pedicle clamping and is associated with an increased risk of complications and worse posthepatectomy liver function.[47] More recently, we have explored mitochondrial function and biogenesis in two-stage hepatectomies with portal vein ligation and confirmed these findings.[50] We found strong and significant correlations between deteriorating mitochondrial energy metabolism and several markers of postoperative liver function, confirming our previous work. Moreover, volumetric regeneration of the liver remnant was also strongly correlated with improved energetic metabolism. Furthermore, we also demonstrated that liver regeneration is associated with an increased expression of peroxisome proliferator-activated receptor-γ coactivator (PGC-1α), a pivotal regulator of mitochondrial biogenesis.[51] In our opinion, the field of bioenergetics in liver surgery and transplantation deserves further investigation, with emphasis on clinical applications.

13 | HYPERURICEMIA PROTECTS AGAINST LOW BONE MINERAL DENSITY, OSTEOPOROSIS AND FRACTURES: A SYSTEMATIC REVIEW AND META-ANALYSIS[52] (NICOLA VERONESE)

In these 2 years, some papers were published.[53-56] This literature regards the role of uric acid on BMD and fractures and the role of gout in increasing the risk of fracture. Overall, the most recent findings suggest that uric acid is associated with higher BMD values, even if not all the papers available confirmed these findings. The papers published in the two last years advanced our knowledge on uric acid and bone metabolism in some populations, such as diabetics and Asians. Finally, some newer papers proposed a role of gout, a pathological excess of uric acid in the joints, in increasing the risk of fractures.

14 | DECREASED SERUM PCSK9 LEVELS AFTER ISCHAEMIC STROKE PREDICT WORSE OUTCOMES[57] (FEDERICO CARBONE AND FABRIZIO MONTECUCCO)

In the 2 years following the publication of the study "Decreased serum PCSK9 levels after ischaemic stroke predict worse outcomes",[57] no other clinical studies specifically addressed the role of serum levels of these molecules in postischaemic brain injury. Rather, large randomized clinical trials emphasized the lipid-lowering effects of monoclonal antibodies inhibiting PCSK9 to prevent adverse cardiovascular events, such as ischaemic stroke.[58] However, PCSK9 was suggested to potentially induce pleiotropic activities including a negative control on the inflammatory response.[59] In addition, PCSK9 is constitutively expressed within the brain and may affect neuronal development and apoptosis.[60] The lack of knowledge in PCSK9-related pathophysiology may partially explain the controversial effects of PCSK9 inhibitors on postischaemic inflammatory response.[61] A better understanding of PCSK9 biology is mandatory to address those questions and ensure a safety use of its inhibitors.

15 | ANTI-ApoA-1 IgG SERUM LEVELS PREDICT WORSE POSTSTROKE OUTCOMES[62] (FEDERICO CARBONE AND FABRIZIO MONTECUCCO)

In the 2 years following the publication of the study "Anti-ApoA-1 IgG serum levels",[62] no other clinical studies specifically investigated the role of those autoantibodies in the pathophysiology of acute ischaemic stroke. Rather, anti-ApoA-1 IgG are increasingly emerging as useful biomarkers of cardiovascular risk. Their levels independently predict both coronary artery disease (CAD) and all-cause mortality in the general population.[63-65] Noteworthy, genomewide association studies (GWAS) identified two loci potentially involved in the risk associated with anti-

ApoA-1 IgG. The association with receptor-like 3 polymorphisms (a susceptibility gene involved in autoimmune diseases) may suggest an intriguing link between preclinical autoimmunity and mortality risk.[64] Similarly, the association between anti-ApoA-1 IgG and CAD seems to be strongly modulated by polymorphisms of CD14,[65] already recognized as effector of pro-inflammatory response mediated by anti-ApoA-1 IgG.[66] Although preliminary, those data might attract the interest towards the role of preclinical autoimmunity in CV risk.

16 | ACUTE CALCIUM KINETICS IN HAEMODIALYSIS PATIENTS[67] (MARKUS PIRKLBAUER)

A longitudinal observational study by Tagawa et al[68] evaluated the association of higher dialysate calcium (DCa), >3.0 vs 2.5 mEq/L, with cardiovascular events (CV) and found an increased risk for myocardial infarction (MI) with the use of higher DCa among diabetic haemodialysis (HD) patients. Statistical analysis revealed that the association of higher DCa and MI could not be explained trough an effect of DCa on albumin-corrected serum calcium and iPTH levels (pre-HD) but rather trough an effect on the intradialytic change in serum calcium levels, suggesting a causal link between acute calcium buffer capacity during haemodialysis and CV events. These findings confirm the clinical relevance of a rapidly exchangeable calcium pool counteracting acute serum calcium deviations in the event of high intradialytic Ca mass balance. By linking reduced calcium buffer capacity with low bone turnover, the study additionally corroborates an involvement of bone in acute extracellular calcium regulation.

17 | β-BLOCKERS ARE ASSOCIATED WITH DECREASED LEUCOCYTE-PLATELET AGGREGATE FORMATION AND LOWER RESIDUAL PLATELET REACTIVITY TO ADENOSINE DIPHOSPHATE AFTER ANGIOPLASTY AND STENTING[69] (THOMAS GREMMEL)

In the recently published PLATE-BLOCK study, 1100 acute coronary syndrome (ACS) patients on dual antiplatelet therapy with aspirin and ticagrelor were randomized in a 1:1 fashion to the nonselective β-blocker carvedilol (n = 50) and the selective β1-blocker metoprolol (n = 50) at the maximum tolerated dose. Platelet aggregation in response to epinephrine and adenosine diphosphate (ADP) was assessed by light transmission aggregometry in all patients at randomization and 1 month thereafter. At 1 month, patients on carvedilol showed significantly lower epinephrine-inducible platelet aggregation and a trend towards lower ADP-inducible platelet aggregation than patients receiving metoprolol, suggesting stronger anti-aggregatory effects of carvedilol.[70] These data reinforce our findings of decreased on-treatment platelet reactivity in patients on β-blocker therapy[69] and show that the anti-aggregatory effects of carvedilol are also present in ticagrelor-treated ACS patients.

18 | EXCESSIVE BLOOD PRESSURE INCREASE WITH EXERCISE AND RISK OF ALL-CAUSE MORTALITY AND CARDIAC EVENTS[71] (MARÍA C. BOUZAS-MOSQUERA AND ALBERTO BOUZAS-MOSQUERA)

The association of an excessive blood pressure increase with exercise (ie, an increase in systolic blood pressure with exercise ≥95th percentile) with lower risk of subsequent events[71] in patients with known or suspected coronary artery disease has been consistently verified even in those with baseline hypertension.[72] Nonetheless, this negative association, also confirmed in another study on a Japanese population,[73] might depend on peak VO2, such that the prognostic value of blood pressure response might be limited in patients with preserved exercise capacity.[73] In addition, a hypertensive response with exercise (defined as a systolic blood pressure ≥220 mm Hg during the test) has also been associated with lower risk of echocardiographic myocardial ischaemia.[74] These findings might be mediated mainly by the degree of exercise-induced increase in cardiac output, which is a main determinant of blood pressure response and may be blunted or even reversed in the presence of significant coronary artery disease.

19 | PCSK9 IN DIABETIC KIDNEY DISEASE[75] (BEATRIZ FERNANDEZ-FERNANDEZ AND MARIA DOLORES SANCHEZ-NIÑO)

Serum PCSK9 were shown to predict cardiovascular events and PCSK9 inhibitors improved outcomes in at least some diabetic populations. In patients at high cardiovascular risk, PCSK9 positively and dose-dependently correlated with atorvastatin dosage, and this effect was magnified in diabetics.[76] Additionally, in diabetic patients with pathological albuminuria enrolled in the large DIABHYCAR study, plasma PCSK9 tertiles were associated with the incidence

of cardiovascular events.[77] Although this was not replicated in the smaller SURDIAGENE cohort that enrolled patients with milder albuminuria,[77] the potential for serum PCSK9 to stratify patients who may benefit from PCSK9 inhibitors should be further explored. In this regard, in post hoc analyses of RCTs, PCSK9 inhibitors reduced cardiovascular events and LDL-cholesterol in diabetic patients[78,79] and phase 3 trials have been designed to specifically evaluate the lipid-lowering efficacy and safety of PCSK9 inhibitors in patients with type 2 diabetes mellitus and dyslipidemia.[80]

20 | PRKG1 AND GENETIC DIAGNOSIS OF EARLY-ONSET THORACIC AORTIC DISEASE[81] (ALEJANDRO BLANCO-VEREA AND MARÍA BRION)

Since the publication of our work where we presented a previously described variant in the PRKG1 gene as a cause of nonsyndromic familial aortic disease (NSAD),[81] no new work describing causal variants in this gene has been published. However, the application of the subsequent published guidelines of the American College of Medical Genetics and Genomics-Association for Molecular Pathology (ACMG-AMP) for the interpretation of genetic variants[82] reinforces the variant classification as pathogenic and therefore the consideration of the PRKG1 gene as a strong candidate gene for gen-based diagnosis of NSAD. Using the "Sherloc" refinement criteria for classification,[83] the variant continues being considered pathogenic, adding up to 5 points of evidence of pathogenicity, considering population frequency, observations in affected and functional evidence. Supporting this consideration, since the publication of the paper, the PRKG1 variant has been described in ClinVar[84] as pathogenic two additional times by different laboratories.

21 | EFFECT OF ENDOTHELIN-1 AND ENDOTHELIN RECEPTOR BLOCKADE ON THE RELEASE OF MICROPARTICLES[85] (CHRISTIAN JUNG AND MICHAEL LICHTENAUER)

In our previous article, we described that endothelin induced the release of endothelial microparticles (EMP) and that endothelin receptor blockers abolished EMP release in vitro. However, in patients with diabetes, bosentan did not affect EMP levels.[85] Recently, we have determined that staying at 2978 m above sea level resulted in a significant decrease of EMP levels. Still, the additional intake of the endothelin receptor blocker Macitentan did not influence EMP concentrations nor cardiovascular biomarkers.[86] Furthermore, we investigated EMP levels in patients with severe degenerative aortic stenosis undergoing transcatheter aortic valve implantation (TAVI). Of note, the TAVI procedure also led to a significant decline in EMP levels, likely via reduction in pressure gradients and consequently reduced turbulent flow.[87] What has come more in the focus is what is stored inside microparticles as potential additional messengers. MicroRNAs have been in the centre of investigation in a broad spectrum of diseases (eg, diabetes) and might shed new light on endothelial signalling mechanisms in these disease conditions.[88]

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CONFLICT OF INTEREST

None.

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APPENDIX 1: STATEMENTS MADE IN THE CONCLUSIONS OF THE ABSTRACT OF ORIGINAL ARTICLES PUBLISHED BY THE EUROPEAN JOURNAL OF CLINICAL INVESTIGATION IN 2016 AND CURRENT STATUS FOR EACH STATEMENT AS JUDGED BY THE AUTHORS OF EACH ORIGINAL STUDY

		Current status for the statement (total number of statements, N = 25)				
References	Statements made in 2016	Reinforced n = 14	Modified n = 0	Weakened n = 1	No new evidence n = 8	Other n = 2
1	There is no evidence of liver or kidney injury in adolescent runners participating in a standard marathon run.	X[a]				
4	Continuous-flow ventricular assist device (VAD) implantation resulted in a significantly better clinical outcome than pulsatile flow VAD implantation.	X				
9	The hGRαT556I causes Chrousos syndrome by impairing multiple steps of the glucocorticoid signal transduction pathway.					X[b]
13	Myeloperoxidase (MPO) levels associate with the dipping pattern and pulse wave velocity.				X	
	Among overweight/obese children, an association exists between MPO and renal function.					X[c]
18	We observed a lower intention to coronary intervention in elderly women compared with men.	X				
	The distribution of risk factors in elderly women and men who did not undergo coronary intervention was similar and therefore seemed not to be causal for the gender gap although the benefit of any coronary interventions was even higher in elderly women.	X				
22	The characteristics of the Asian hypertensive patients with diastolic hypertension can present a favourable metabolic response to the short-term hydrochlorothiazide treatment.				X	
24	Elevated levels of circulating galectin-3 are strongly associated with premature myocardial infarction.				X	
	Galectin-3 might serve as link between dyslipidaemia as driving force of plaque formation with inflammation as initiator of plaque rupture in patients with premature acute myocardial infarction.				X	
28	Using charts from other populations (including INTERGROWTH-21st) may be unrepresentative of local populations and lead to misclassification of foetal growth status.	X				
33	Nonruptured aneurysms are associated with increased extracellular signal-related kinase activation while ruptured aneurysms are not.	X				
	Extracellular signal-related kinase was not related to total matrix metalloproteinase-2 expression.			X		

(Continues)

APPENDIX I (Continued)

References	Statements made in 2016	Current status for the statement (total number of statements, N = 25)				
		Reinforced n = 14	Modified n = 0	Weakened n = 1	No new evidence n = 8	Other n = 2
38	Bilirubin is modestly increased in response to higher glucocorticoid exposure in humans, in conjunction with lower alkaline phosphatase and aspartate aminotransferase activities, which are supposed to represent biomarkers of a pro-inflammatory state and enhanced liver fat accumulation.	X				
43	Aliskiren improved endothelial progenitor cell function from patients with type 2 diabetes mellitus in a dose-dependent manner probably via the (pro) renin receptor-related and vascular endothelial growth factor/stromal cell-derived factor-1α (VEGF/SDF-1α) related mechanisms.				X	
47	There is a relationship between mitochondrial function, duration of hepatic pedicle clamping and clinical outcome after hepatectomy. Mitochondrial bioenergetics can potentially translate into clinical practice, assisting in earlier diagnosis of postoperative liver dysfunction, and as a target for future pharmacological therapies.	X				
52	Hyperuricemia was found independently associated with BMD and fractures, supporting a protective role for uric acid in bone metabolism disorders.	X				
57	Decreased serum PCSK9 levels after ischaemic stroke predict worse outcomes.				X	
62	Anti-ApoA-1 IgG serum levels predict worse poststroke outcomes.				X	
67	Our data strongly suggest the existence of a rapidly exchangeable calcium pool that counteracts acute serum calcium deviations in haemodialysis patients. This study provides, for the first time, experimental evidence for the involvement of bone in acute extracellular calcium regulation in vivo.	X				
69	β-Blockers are associated with decreased leucocyte-platelet aggregate formation and lower on-treatment residual platelet reactivity to adenosine diphosphate in patients with dual antiplatelet therapy following angioplasty and stenting.	X				
71	An excessive blood pressure increase with exercise was associated with a significantly lower risk of mortality and major acute coronary events in patients with known or suspected coronary artery disease referred for stress testing.	X				
75	In diabetic kidney disease (DKD), therapy with lipid-lowering drugs and specially the fibrate/statin combination were independently associated with higher PCSK9 levels. The biomarker potential of PCSK9 levels to identify DKD patients that may benefit from anti-PCSK9 strategies should be studied.	X				

(Continues)

APPENDIX I (Continued)

References	Statements made in 2016	Current status for the statement (total number of statements, N = 25)				
		Reinforced n = 14	Modified n = 0	Weakened n = 1	No new evidence n = 8	Other n = 2
81	This was the second time PRKG1 was associated with thoracic aortic disease, highlighting and reaffirming it as a strong candidate for gene-based diagnosis of nonsyndromic early-onset cases.	X				
85	Our in vitro results suggest that endothelin-1 (ET-1) stimulates the release of endothelial microparticles (EMP) from human umbilical vein endothelial cells via a receptor-dependent mechanism. Co-incubation with an endothelin receptor blocker abolished ET-1-dependent EMP release. However, treatment with bosentan for 4 wk failed to alter EMP levels in patients with type 2 diabetes mellitus (T2DM). Other factors seem to have influenced EMP release in patients with T2DM independent of ET-1 receptor-mediated mechanisms.				X	

[a]However, it cannot be excluded that with increasing age and/or with repeated marathon running kidney injury may become relevant.

[b]These data show that many cases of Chrousos syndrome may be underdiagnosed because of a mild clinical phenotype. Moreover, several other yet unidentified factors may participate in the pathogenetic mechanisms of Chrousos syndrome.

[c]Myeloperoxidase was not significantly associated with renal function in a study involving older children with obesity or type 1 diabetes and healthy controls.[16] However, this analysis was not performed separately for obese children and glomerular filtration rate (GFR) was calculated using a different formula (Bouvet formula)[16] from that used in our study (Zappitelli combined formula).[13] The Bouvet formula, but not the Zappitelli combined formula, appears to yield an underestimation of GFR values in comparison with the reference standard for GFR (inulin clearance) and is limited by the use of creatinine values assessed by the Jaffe method.[17]