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REPORT

Research update for articles published in EJCI in 2017

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1 | HEPATIC CHEMERIN MRNA EXPRESSION IS REDUCED IN HUMAN NONALCOHOLIC STEATOHEPATITIS¹ (CHRISTA BUECHLER)

No new evidence on the regulation of hepatic chemerin expression by liver X receptor exists. However, there is one recent study which described an insignificant increase in hepatic chemerin mRNA levels in patients with a body mass index ≥ 40 kg/m² compared to patients with a body mass index (BMI) < 40 kg/m². Chemerin mRNA was detected in the liver of all patients, and was higher in patients with hepatic steatosis. Chemerin mRNA expression was not related to fibrosis and inflammation stages.² It should be noted that immunohistochemistry detected chemerin protein in 52% of the livers analysed.² Hepatic chemerin protein was not associated with histopathological features of nonalcoholic steatohepatitis (NASH).² Current data on the expression of chemerin in the liver are not concordant.³ Further research is needed to clarify the regulation of chemerin expression in the liver and to evaluate its role in NASH.

2 | CARVEDILOL AND ANTIOXIDANT PROTEINS IN A TYPE I DIABETES ANIMAL MODEL⁴ (PAULO OLIVEIRA AND PIERO PORTINCASA)

In the paper by Diogo et al,⁴ we showed that the β -blocker carvedilol increased the content of antioxidant enzymes catalase in the heart and skeletal muscle, as well as superoxide dismutase 1 and 2 in the skeletal muscle of a chemical model for hyperglycaemia, the streptozotocin-injected animal. The translational value of this paper was that carvedilol may be beneficial in patients with uncontrolled diabetes, decreasing the progression of diabetic cardiomyopathy or hyperglycaemia-related oxidative stress in skeletal muscle. Zheng et al later confirmed these findings in the same rat model,⁵ and demonstrated that oral carvedilol suppressed myocardial inflammatory response, fibrosis, P66^{shc}-mediated oxidative stress and apoptosis in cardiac muscle. Also, in a high-fat

diet model of type 2 diabetes mellitus and obesity, Wang et al⁶ showed that β 2-adrenergic receptor inhibition by carvedilol resulted in decreased contractile dysfunction, although the authors could not demonstrate the relationship with decreased oxidative stress.

3 | ANTIBIOTIC RESISTANCE IN HEALTHCARE-RELATED AND NOSOCOMIAL SPONTANEOUS BACTERIAL PERITONITIS⁷ (FELIX GOESER AND PHILIPP LUTZ)

Our statement “Resistance to initial antibiotic treatment was associated with increased mortality”,⁷ has been reinforced by several studies. In two separate analyses of patients included into the CANONIC database focussing on bacterial infections as trigger and consequence of acute-on-chronic liver failure⁸ and on prevalence and impact of multi-drug resistant bacteria,⁹ inappropriate empirical antibiotic treatment was an independent predictor of mortality. In addition to replicating this finding, a large international study of patients with liver cirrhosis¹⁰ supported our second statement⁷: “With resistance to cephalosporins being frequent, piperacillin–tazobactam or carbapenems might be preferred as treatment of spontaneous bacterial peritonitis”, by reporting susceptibility to piperacillin-tazobactam and carbapenems higher than 70% and 85%, respectively. While in these studies, spontaneous bacterial peritonitis (SBP) accounted for about 25% of infections, another investigation focussing exclusively on SBP reinforced the second statement by reporting susceptibility to piperacillin-tazobactam in 91% of Gram-Negative and 66% of Gram-Positive bacteria.¹¹

4 | STENT-INDUCED TRACHEAL STENOSIS CAN BE PREDICTED BY IL-8 EXPRESSION IN RABBITS¹² (FRANCISCO RODRIGUEZ-PANADERO AND ELENA ARELLANO-ORDEN)

Following publication of our above article,¹² we have extended our research on this field and we are currently investigating the release of metallic elements from the stents into the tracheal

surrounding tissue, including nickel, cobalt, titanium and others. Lixiviation of those metallic elements into culture medium *in vitro* was previously demonstrated by us in a recent work (in press), and preliminary results from our current *ex vivo* (rabbits) study suggests that most of the metallic elements spread from the stents into the tracheal tissue, then contributing to the significant inflammation and fibrotic processes that were observed both by tracheoscopy and at autopsy.¹³⁻¹⁶ We plan to have a new manuscript on this topic prepared by the end of this year, and also hope to have that paper accepted in the European Journal of Clinical Investigation (EJCI), then advancing further in this exciting line of research.

5 | ALAMANDINE ABROGATES NEUTROPHIL DEGRANULATION IN ATHEROSCLEROTIC MICE¹⁷ (FEDERICO CARBONE AND FABRIZIO MONTECUCCO)

In the 2 years following the publication of the study “Alamandine abrogates neutrophil degranulation in atherosclerotic mice”,¹⁷ we were unable to find any clinical studies confirming our results in mice. However, alamandine was increasingly described as a cardioprotective compound. By counteracting cardiomyocyte hypertrophy, cardiac fibrosis, sympathetic activity¹⁸ and pro-inflammatory macrophage activation,¹⁹ treatment with alamandine was shown to effectively prevent cardiac hypertrophy, dilated cardiomyopathy and even myocardial reperfusion injury in experimental models.²⁰

Furthermore, alamandine was shown to interfere with other intracellular signalling pathways with effect on hyperhomocysteinemia and leptin expression. Although a role on neutrophil degranulation was no longer investigated, alamandine is emerging as an inhibitor of the renin-angiotensin-aldosterone system with potential beneficial effect on cardiovascular system. In light of this, alamandine deserves further studies to clarify potential translation of experimental evidence into clinical practice.

6 | ALKALINE PHOSPHATASE AND PROGNOSIS IN PATIENTS WITH CORONARY ARTERY DISEASE²¹ (GJIN NDREPEPA)

Our study that included 5540 patients with angiography-proven coronary artery disease (CAD) showed that elevated alkaline phosphatase (ALP) activity was independently associated with increased risk of mortality up to 3 years after percutaneous coronary intervention. Since its publication, additional evidence has gathered that elevated ALP activity in patients with CAD is associated with increased risk of

mortality in prospective cohort studies²² and patients with acute coronary syndromes²³ or acute ischaemic stroke.²⁴ Other studies have reported an association between ALP and atherosclerotic risk.^{25,26} A recent study in a mouse model of familial hypercholesterolaemia showed that overexpression of tissue-nonspecific ALP in endothelial cells accelerates coronary atherosclerosis through an interaction between primary intimal calcification in the form of subendothelial nodules and hypercholesterolaemia increasing lipid deposition into atherosclerotic lesions.²⁶ In subjects free of clinical cardiovascular disease, elevated ALP levels were positively and independently associated with coronary artery calcium—a surrogate of coronary atherosclerosis.²⁵

7 | ANTIHYPERGLYCAEMIC DRUGS USE AND NEW-ONSET ATRIAL FIBRILLATION IN ELDERLY PATIENTS²⁷ (YI-SHENG LIOU AND GWO-PING JONG)

We had earlier demonstrated that patients who were administered dipeptidyl peptidase 4 (DPP4) inhibitors had a lower risk of developing new-onset atrial fibrillation (NAF) than nonusers among the elderly.²⁷ Simultaneously, another research group in Taiwan from which they identified 16 017 patients in the cohort of DPP4 inhibitor users and 74 863 patients in the cohort of DPP4 inhibitor nonusers and reported that DPP4 inhibitor therapy is associated with a decreased risk of developing NAF.²⁸ However, another study identified 401 linagliptin users who had acute coronary syndrome or acute ischaemic stroke and 802 controls (matched with patient characteristics, baseline comorbidities, medication prescribed 90 days since indexed hospitalization and index year and month by propensity score).²⁹ They concluded that the risk of developing NAF was neutral between linagliptin users and nonusers. Thus, it is possible that DPP4 inhibitors have not been shown to increase the risk of developing NAF.

8 | REAL WORLD STROKE PREVENTION STRATEGIES IN NONVALVULAR ATRIAL FIBRILLATION IN PATIENTS WITH RENAL IMPAIRMENT³⁰ (KADIR UĞUR MERT AND GURBET ÖZGE MERT)

Nowadays, real-world registries and the experiences have increased with the more widespread use of non-vitamin K oral anticoagulants (NOACs). But, renal impairment (RI) is still making management challenging in patients with atrial

fibrillation (AF) due to struggles for warranting balance between risks of ischaemic stroke and haemorrhages. Patients with RI have increased prevalence of AF and other associated risk factors for stroke and also have increased bleeding risk.^{31,32} In a recent registry (ORBIT AF, n = 9019),³³ similar to our RAMSES (n = 6273) study's results,³⁴ it was revealed that patients with chronic kidney disease (CKD) are less likely to receive oral anticoagulants. Compared with warfarin, all four NOACs showed consistent efficacy and safety in patients with mild to moderate CKD.³¹ In an observational study of >25 000 patients with AF on dialysis showed that the discontinuation rates were high, and only one-third of patients were taking the anticoagulant 12 months after the initial prescription.³⁵

9 | MEDITERRANEAN DIET DECREASES ADOLESCENT WAIST CIRCUMFERENCE³⁶ (FLORA BACOPOULOU AND VASILIKI EFTHYMIU)

Following publication of our study³⁶ in a large adolescent sample, more evidence has accumulated, reinforcing its conclusion. We randomly selected 20 adolescents aged 12-17 years with overweight or obesity (mean \pm SD body mass index 28.9 ± 5.7 kg/m²), which were followed up at the tertiary Centre for Adolescent Medicine, over the past 2 years. Adolescents and their parents attended monthly face-to-face sessions with an adolescent medicine paediatrician and a registered dietician, aiming to improve adolescents' adherence to Mediterranean diet and promote a healthy lifestyle. At baseline, adolescents' (mean \pm SD) waist circumference (WC) was 85.1 ± 11.2 cm and Mediterranean Diet Quality Index in children and adolescents (KIDMED) score was 5.0 ± 2.5 . After 2 years of follow-up, adolescents' KIDMED score increased to 6.1 ± 2.8 ($P = .024$) and WC decreased significantly to 80.7 ± 8.5 cm ($P = .041$). More evidence³⁷ published in the meanwhile also confirms the statement that multilevel-multidisciplinary interventions that increase adherence to Mediterranean diet are associated with decreased WC in adolescence.

10 | MULTIBIOMARKER ANALYSIS IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION³⁸ (CHRISTIANA SCHERNTHANER AND MICHAEL LICHTENAUER)

Elevated serum levels of soluble suppression of tumorigenicity (sSTS), growth-differentiation factor-15 (GDF-15), soluble urokinase plasminogen activator receptor (suPAR)

and heart-type fatty acid-binding protein (H-FABP) have been shown as powerful predictors for mortality and risk of heart failure in patients with acute myocardial infarction (AMI)³⁹⁻⁴¹ and help for a precise diagnostic in patients with cardiomyopathy.⁴² Published transmembrane receptor sST2-assisted flowcharts offer a practical tool to differentiate AMI and heart failure in the emergency department.⁴³ Animal models underline the role of ST2 in myocardial remodelling. Metformin and omega-3 fatty acids have been shown to modulate the ST2/Interleukin33 pathway and may reduce the risk of adverse heart failure outcomes after AMI.

11 | DOWNREGULATION OF CHOLESTERYL ESTER TRANSFER PROTEIN BY GLUCOCORTICOIDS: A RANDOMISED STUDY ON HIGH-DENSITY LIPOPROTEIN⁴⁴ (ROBIN PF DULLAART AND FRANK G. PERTON)

The cholesteryl ester transfer process, which is mediated by the cholesteryl ester transfer protein (CETP), provides a key step in plasma lipoprotein metabolism, with large very low-density lipoproteins (VLDL) being preferred acceptors of cholesteryl esters from high-density lipoprotein (HDL) particles.^{45,46} We have shown that glucocorticoids are able to downregulate CETP mRNA expression in a human macrophage cell line.⁴⁴ In keeping with these in vitro results, an increased hydrocortisone dose decreases plasma CETP activity and increases HDL size in hypopituitary patients.⁴⁴ Since the appearance of our paper, no new evidence has become available to reinforce or modify our findings. Notably, however, lowering circulating CETP by pharmacological CETP inhibition could reduce the risk of diabetes development.⁴⁷ Hence it would be interesting to delineate whether the extent to which glucocorticoids inhibit CETP impacts on diabetes risk in future studies.

12 | MONOCYTE COUNT AT ONSET PREDICTS POSTSTROKE OUTCOMES DURING A 90-DAY FOLLOW-UP⁴⁸ (FEDERICO CARBONE AND FABRIZIO MONTECUCCO)

In the 3 years following the publication of the study "Monocyte count at onset predicts poststroke outcomes during a 90-day follow-up",⁴⁸ prognostic relevance of monocytes (assessed as decreased lymphocyte-to-monocyte ratio) was later confirmed in acute ischaemic stroke. Noteworthy, a relevant prognostic accuracy was also maintained during the first 7 days after acute event.^{49,50} This point is very intriguing

as it suggests how monocyte recruitment and activation might have a critical relevance not only in the acute inflammatory phase but also in the recovery process following an acute ischaemic stroke. Further indicating an involvement in brain injury, prognostic relevance of monocytes count was also demonstrated in spontaneous intracerebral haemorrhage.⁵¹ Although any therapeutic perspective remains highly speculative, the inhibition of monocyte/macrophage polarization by soluble epoxide hydrolase was shown to improve neurological outcome in a rat model of ischaemic stroke.⁵²

13 | ADRENOMEDULLIN AND GALANIN RESPONSES TO ORTHOSTASIS IN OLDER PERSONS⁵³ (NANDU GOSWAMI AND JAMES BROADBENT)

While plasma galanin and adrenomedullin responses to head-up tilt and lower body negative pressure have been extensively studied,⁵⁴⁻⁵⁷ to what extent short-arm human centrifugation (SAHC)^{54,56} affects these responses is not known. SAHC is routinely used to simulate central hypovolaemia. Our recent work has investigated how applying varying gradients of accelerations (ΔGz) affects galanin and adrenomedullin in subjects⁵⁸ which was achieved by shifting the rotation axis during centrifugation. Our findings observed that: (a) baseline galanin values could predict development of presyncope in subjects, and (b) increases in galanin and adrenomedullin levels occur in subjects during elevated levels of central hypovolaemia thus suggesting that galanin and adrenomedullin are important for coping with such stressors.

14 | VITAMIN D PREDICTORS IN POLYCYSTIC OVARY SYNDROME: A META-ANALYSIS⁵⁹ (FLORA BACOPOULOU AND EVANGELIA CHARMANDARI)

Since our meta-analysis, further research in women with polycystic ovary syndrome (PCOS) also stresses the relevance of vitamin D status with luteinizing hormone and metabolic syndrome components. However, a positive association of circulating vitamin D with plasma glucose concentrations is not supported by recent data. More specifically, a large epidemiologic study by Krul-Poel et al⁶⁰ demonstrated that low serum 25-hydroxyvitamin D concentrations in women with PCOS were significantly associated with higher insulin resistance (independent of BMI, season and ethnicity) and low high-density lipoprotein (HDL) cholesterol and apolipoprotein A1 concentrations. In another study,⁶¹ vitamin D-deficient women with PCOS had significantly higher glucose, fasting insulin and Homeostatic

Model Assessment of Insulin Resistance (HOMA-IR) than controls, whereas PCOS women with metabolic syndrome had lower circulating 25-hydroxyvitamin D concentrations than those without metabolic syndrome. Moreover, 25-hydroxyvitamin D concentrations correlated positively with HDL cholesterol in all subjects and negatively with the luteinizing hormone/follicle-stimulating hormone ratio in women with PCOS.

15 | A NOVEL CLUSTER OF PATIENTS WITH FAMILIAL MEDITERRANEAN FEVER IN SOUTHERN ITALY⁶² (LEONILDE BONFRATE AND PIERO PORTINCASA)

We recently described a novel cluster of patients with FMF⁶² and suggested that the Apulia region in southern Italy represents a new endemic area for familial Mediterranean fever (FMF). The compound heterozygosity for MEFV variants E148Q/R761H was largely prevalent in our population. Data reinforce the evidence that FMF-causative mutations have a peculiar geographic distribution, while symptom severity is mostly dependent on ethnic background. In fact, in the FMF cohort described by Cekin et al,⁶³ the R761H had a modest 0.9% frequency. Furthermore, in the web-based collection of genotype-phenotype association recently published by Papa et al,⁶⁴ the compound heterozygotes E148Q/R761H show a much earlier onset of symptoms, compared to the onset observed in our patients with identical genotype, recently discussed by Stella et al.⁶⁵ Therefore, the recent literature reinforces our previous report suggesting that FMF clinical presentation can be highly variable and have a population specific genetic and morbidity.

16 | RELATIONSHIP BETWEEN FAMILY HISTORY OF TYPE 2 DIABETES AND SERUM FIBROBLAST GROWTH FACTOR 21⁶⁶ (GREGGORY R. DAVIS)

Updated evidence has been limited as it relates to healthy patients. One study found that serum fibroblast growth factor 21 (FGF21) was an effective independent biomarker for diabetes prediction.⁶⁷ However, additional research has generally suggested that elevated serum FGF21 is associated with pre-existing medical conditions. Ong et al found that FGF21 levels were higher in patients with metabolic syndrome compared to those without.⁶⁸ Similarly, Baek et al found that FGF21 levels were higher found in obese children and were correlated with Homeostatic Model Assessment of

Insulin Resistance (HOMA-IR), indicating FGF21 could be a predictive biomarker for obesity-induced insulin resistance.⁶⁹ Thus, FGF21 may still be a useful predictive marker of type 2 diabetes, but this may be specific to patients with pre-existing conditions associated with metabolic syndrome. This would be similar to the findings of Shen et al who found that elevated serum FGF21 was a predictive marker of adverse cardiovascular events in coronary artery disease patients.⁷⁰

17 | CORONARY ARTERY DISEASE AND RISK OF ADVERSE CARDIAC EVENTS AND STROKE⁷¹ (KEVIN KRIS WARNAKULA OLESEN AND MICHAEL MAENG)

We have further examined the association between extent of coronary artery disease (CAD) and ischaemic stroke after coronary angiography in a large cohort from Western Denmark. The extent of CAD was associated with an incremental risk of ischaemic stroke and thromboembolism (ischaemic stroke/transient ischaemic attack/systemic embolism) in patients without atrial fibrillation and no previous cerebral ischaemia (n = 68 829).⁷² Obstructive multivessel CAD (2 or 3 vessel disease) was associated with a particularly high thromboembolic risk. In patients with atrial fibrillation (n = 12 690), the presence but not the extent of CAD was associated with increased thromboembolic risk.^{73,74} Furthermore, stable CAD is an independent risk factor for thromboembolism and ischaemic stroke in patients with atrial fibrillation and should be included in the “Vascular” component of the CHA2DS2-VASc score.⁷³ Including stable CAD in the CHA2DS2-VASc score would reclassify 3%-6% of angiography patients with atrial fibrillation from low-risk to high-risk patients, potentially requiring oral anticoagulant treatment.

18 | INFLUENCE OF DECISION AIDS ON ORAL ANTICOAGULANT PRESCRIBING AMONG PHYSICIANS: A RANDOMIZED TRIAL⁷⁵ (CRISTIAN BAICUS)

There is no update directly concerning the three statements of the conclusion.

A recent study found that patients prefer pie charts to Cates diagrams, which we used in our study on physicians, for the risk presentation.⁷⁶ We wanted to verify the first two statements on patients, but we acknowledged that the patients with atrial fibrillation did not know why they took antithrombotic therapy. Therefore, first we made a study to validate the Romanian version of a questionnaire for the assessment of the shared decision-making (SDM),⁷⁷ we assessed the SDM

process as perceived by the patients, using this questionnaire,⁷⁸ and we assessed the Romanian patients' awareness concerning the complications and treatment of atrial fibrillation (not yet published). Only 55% of them knew that they were in danger of ischaemic stroke, while 62% knew that the antithrombotic medication prevented stroke.

19 | LIVER ENZYMES ARE NOT DIRECTLY INVOLVED IN ATRIAL FIBRILLATION: A PROSPECTIVE COHORT STUDY⁷⁹ (RUDOLPH SCHUTTE)

Since reporting that the relationship between incident atrial fibrillation (AF) and the liver enzymes gamma-glutamyl transferase (GGT), alanine transaminase (ALT) and aspartate transaminase (AST) depends on the progression of heart failure as captured by Δ N-terminal pro-brain natriuretic peptide (NT-proBNP),⁷⁹ no other studies reported on AST and ALT. However, the attention moved to GGT.^{80,81} Using the first quartile as reference, Lee et al⁸⁰ observed an independent association between AF and GGT in 266,550 participants after a median follow-up of 8 years. This observation was independent of baseline prevalence of heart failure, but the progression of heart failure was not captured. Similarly, Ndrepepa et al⁸¹ observed this independent relationship in 5501 patients with coronary artery disease. The authors also adjusted for baseline left ventricular ejection fraction (which was lower in the AF group), but again not progression. The mechanistic explanations on these observational findings remain challenging and the most popular seems to be GGT's relationship with oxidative stress. We expect the AF-GGT relationship to be nullified when adjustment is made for oxidative stress, discouraging the use of GGT (or any liver enzymes) as markers of atrial fibrillation.

CONFLICT OF INTEREST

None.

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APPENDIX

TABLE A1 Statements made in the Conclusions of the Abstract of original articles published by the European Journal of Clinical Investigation in 2017 and current status for each statement as judged by the authors of each original study

References	Statements made in 2017	Current status for the statement				
		Reinforced n = 14	Modified n = 4	Weakened n = 1	No new evidence n = 5	Other n = 1
1	Chemerin mRNA is reduced in the liver of nonalcoholic fatty liver disease patients, and liver X receptor seems to have a role herein.		X ^a			
4	Based on data showing modulation of the antioxidant network in the heart, carvedilol may be beneficial in diabetic patients without advanced disease complications, delaying their progression.	X				
7	Resistance to initial antibiotic treatment was associated with increased mortality.	X				
7	With resistance to cephalosporins being frequent, piperacillin-tazobactam or carbapenems might be preferred as treatment of spontaneous bacterial peritonitis.	X				
12	The cobalt-based stent had the highest incidence of tracheal inflammation and stenosis.	X				
12	On the other hand, the paclitaxel-eluting nitinol stent did not prevent those complications and provoked a marked reaction compared with the bare nitinol stent.					X ^b
	Early increase in IL-8 expression in blood after stent implantation could predict development of tracheal stenosis in rabbits.	X				
17	These results suggest that treatment with the Mas-related G-coupled receptor type D agonist alamandine led to a reduced release of neutrophil granule products, potentially interfering with pro-atherosclerotic neutrophil activation.				X	
21	In patients with coronary artery disease, elevated alkaline phosphatase activity was independently associated with the risk of 3-year all-cause mortality.	X				

(Continues)

TABLE A1 (Continued)

References	Statements made in 2017	Current status for the statement				
		Reinforced n = 14	Modified n = 4	Weakened n = 1	No new evidence n = 5	Other n = 1
27	In this population, use of dipeptidyl peptidase 4 inhibitor was associated with a low risk of new-onset atrial fibrillation.			X		
27	Insulin use was associated with a significant increase in the risk of new-onset atrial fibrillation during the long-term follow-up.				X	
30	RAMSES study showed that one-third of the patients with nonvalvular atrial fibrillation had renal impairment in the real-world setting.	X				
30	Although it is mandatory in most of the patients with concomitant nonvalvular atrial fibrillation and renal impairment, nearly one-third of these patients did not receive any anticoagulant therapy.	X				
36	Increased adherence to mediterranean diet was associated with decreased waist circumference, indicating a potential of multicomponent – multilevel school-based interventions to combat adolescent abdominal obesity.	X				
38	Plasma levels of novel biomarkers were significantly elevated (soluble suppression of tumorigenicity, growth-differentiation factor-15, soluble urokinase plasminogen activator receptor, and heart-type fatty acid-binding protein) or inversely downregulated (fetuin A) in patients with acute myocardial infarction compared to a control group with excluded coronary artery disease. Significant correlations with various clinical parameters and standard biochemical markers were found.	X				
44	Glucocorticoids downregulate cholesteryl ester transfer protein (CETP) gene expression in a human macrophage cell system. In line, a higher glucocorticoid replacement dose decreases plasma CETP activity in patients, thereby contributing to higher high-density lipoprotein (HDL) cholesterol and an increase in estimated HDL size.				X	
48	In the overall cohort, monocyte count was an independent predictor of worse poststroke outcome. Although larger trials are needed, monocyte count might be a cheap prognostic parameter in acute ischemic stroke.	X				
53	Adrenomedullin and galanin concentrations were similar between genders and did not change following adoption of the standing posture. To further clarify the roles, these hormones play in orthostatic intolerance, adrenomedullin and galanin concentrations should be assessed in participants who show presyncopal symptoms during an orthostatic challenge.		X ^c			
59	Serum 25-hydroxyvitamin D may be predicted positively by serum calcium and negatively by luteinising hormone in women with polycystic ovary syndrome (PCOS), and negatively by waist-to-hip ratio.	X ^d				
	Serum 25-hydroxyvitamin D may be predicted positively by fasting glucose in both PCOS and non-PCOS women, independently of the presence of obesity.		X ^e			

(Continues)

TABLE A1 (Continued)

References	Statements made in 2017	Current status for the statement				
		Reinforced n = 14	Modified n = 4	Weakened n = 1	No new evidence n = 5	Other n = 1
62	The Apulia region represents a new endemic area for familial Mediterranean fever (FMF). Clinical presentation of FMF can be misleading and requires a complete and early workup to recognise the disease and avoid unjustified surgery. Colchicine remains the gold standard therapy to prevent FMF attacks and fatal long-term complications.	X				
66	Serum fibroblast growth factor 21 (FGF21) is not significantly different between individuals with a family history (FH+) of type 2 diabetes (T2D) and individuals without a family history (FH-) of T2D in young, healthy individuals. Based upon the data of this pilot study, it is unclear whether serum FGF21 can be used as a stand-alone predictive marker for T2D in healthy subjects.	X ^f				
71	The presence and extent of coronary artery disease was associated with an incremental risk of death, cardiac death, and myocardial infarction over a 7-year period.	X				
	The presence and extent of coronary artery disease was associated with an incremental risk of ischaemic stroke over a 7-year period.		X ^g			
75	Risks could be communicated using decision aids with only one graphic. Showing the risk of stroke at 5 years could increase the prescription of oral anti-coagulants to patients with atrial fibrillation. Faced with the same risk of stroke, physicians prescribed less to themselves than to patients.				X	
79	The direct relationship between atrial fibrillation and liver enzymes is absent and depends, at least in part, on the progression of heart failure as captured by N-terminal pro-brain natriuretic peptide.				X	

^aChemerin mRNA and protein were not changed in non-alcoholic steatohepatitis (NASH) liver of very obese patients.

^bAs mentioned in the "Limitations to the study" in our article,¹² dosage of paclitaxel for the stents used in our experiments was designed for intravascular use, and we therefore believe that it was more appropriate for coronary arteries than for airways, since blood flow is more likely to be more efficient than airflow in clearing the paclitaxel delivered by the stent, and dosage for airways should therefore be lower. On the other hand, accumulated evidence suggests that other antiproliferative drugs like everolimus, tacrolimus and others are safer than paclitaxel for intravascular and airways use.

^cThe evidence that has accumulated in the meanwhile modifies this statement, as we observed in our Winter et al (2019) study that: (a) elevated baseline levels of galanin are related to orthostatic tolerance; and that (b) elevated galanin levels aims to support good orthostatic tolerance during centrifugation. For adrenomedullin, however, central mechanisms rather than adrenomedullin distribution predominate when coping with central hypovolemia induced by short-arm human centrifugation. These results suggest that galanin levels increase during elevated levels of central hypovolemia and that adrenomedullin release depends on degree of central hypovolemia induced fluid shifts and a subject's ability to cope with such challenges. Our findings in a recent study identified that upon application of moderate lower body negative pressure to subjects, plasma adrenomedullin increased in males but not in females (Goswami et al, 2019b). This suggests a differential adrenomedullin response to central hypovolemia in males and females.

^dThe evidence that has accumulated in the meanwhile reinforces the statement: "Serum 25-hydroxyvitamin D may be predicted negatively by waist-to-hip ratio and luteinising hormone in women with PCOS."

^eThe evidence that has accumulated in the meanwhile modifies the statement: "Serum 25-hydroxyvitamin D may be predicted positively by fasting glucose in PCOS women" as follows: "a negative association of circulating vitamin D with glucose has been reported in women with PCOS."

^fThe evidence that has accumulated in the meanwhile modifies the statement: "Serum FGF21 is not significantly different between FH+ and FH- in young, healthy individuals. Based upon the data of this pilot study, it is unclear whether serum FGF21 can be used as a stand-alone predictive marker for T2D in healthy subjects that do not exhibit any conditions associated with metabolic syndrome."

^gThe evidence that has accumulated in the meanwhile modifies the statement: "Presence of coronary artery disease (CAD) is associated ischemic stroke irrespective of atrial fibrillation. However, extent of CAD is only associated ischemic stroke risk in patients without atrial fibrillation."