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RESEARCH UPDATE

Research update for articles published in EJCI in 2013

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Comorbidities and survival in obstructive sleep apnoea beyond the age of 50 [1] (Oreste Marrone)

We found that among subjects ≥ 50 years old obstructive sleep apnoea (OSA) severity did not influence survival; nevertheless, OSA treatment was associated with better survival if comorbidities were present at the time of its diagnosis [1]. Recently, two studies have shown improved survival with continuous positive airway pressure (CPAP) treatment among OSA patients ≥ 60 years old, but have not separately analysed data on subjects without comorbidities [2,3]. One investigation in elderly subjects has shown that nocturnal hypoxia was associated with higher apnoea/hypopnoea indices, and increased cardiovascular mortality only among subjects with cardiovascular disease at the time of polygraphic study [4]. Finally, one paper has reported better cardiovascular survival after ischemic stroke among treated, than untreated, OSA subjects aged 63·7 ± 9·1 [5], similar to older studies. In summary, new studies reinforce our conclusions, showing no increase in cardiovascular mortality in aged OSA patients without cardiovascular disease, and improved survival in aged OSA patients with stroke treated with CPAP.

[Correction added after initial online publication on 22 September, 2015: the author name was changed from Georg Goliasc to Georg Goliasch.]

A novel mutation in the albumin gene (c.1A>C) resulting in analbuminemia [6] (Gianluca Caridi and Lorenzo Minchiotti)

In the last 2 years the continuing study of the defects causing congenital analbuminemia (CAA, OMIM # 103600) allowed us to identify the mutations in two analbuminemic individuals: a female new-born from Ankara, Turkey [7], and a young Australian woman of Lebanese origin [8]. In the latter the trait was caused by the Kayseri mutation [c.228_229delAT], whereas a novel c.1652 + 1G>A splicing defect originates the Turkish case. These data confirm that CAA is an allelic heterogeneous disorder, caused by homozygous or, in a single individual, compound heterozygous inheritance of defects in the albumin gene. Most of these defects are unique, but the Kayseri mutation is responsible for about one-third of the cases characterised at the molecular level. An updated list of the known cases and of their causative mutations can be found in the albumin website (http://albumin.org). For a more detailed discussion on the molecular genetics of CAA [9].

Visceral adiposity index is highly associated with adiponectin values and glycaemic disturbances [10] (Shaun Sabico and Nasser M. Al-Daghri)

Our article in visceral adiposity index (VAI) done in Arab adults [10] was extended in children [11] and observed that the associations between VAI and cardiometabolic risk in this population is inferior to body mass index (BMI). The use of a pediatric and non-Caucasian population were opposed by Amato and colleagues, citing that the mathematical index was based on numerical constants derived from healthy, adult Caucasian populations [12] We considered this premise legitimate and await investigations that will come up with a pediatric 'VAI'. In the meantime, the clinical significance of VAI in non-Caucasian populations is starting to accumulate to include other cardiometabolic risk factors like prehypertension [13] and is expected to confirm its role as a good marker of adipose dysfunction, at least in adults [14].

Uric acid and prognosis in angiography-proven coronary artery disease [15] (Gjin Ndrepepa)

In our study that included 13 273 patients with angiographic confirmation of coronary artery disease (CAD) treated with percutaneous coronary intervention, we concluded that uric acid (UA) predicted an increased risk of cardiac and all-cause mortality across all subsets of the patients and that the association between UA and cardiac or all-cause mortality had a 'J-shaped' pattern with lowest risk of death in patients with UA levels between 5·17 and < 6·76 mg/dL. Since its publication, evidence has gathered that elevated UA level is associated CAD and/or increased incidence of cardiovascular adverse events [16–20]. One recent study in which UA was measured in 3315 patients showed that UA was associated with CAD and it was causally related to adverse cardiovascular events, especially sudden cardiac death [16]. In another recent study UA was associated with mortality especially in women over a median of 23-year follow-up [17]. Other studies have shown an association between elevated UA level and CAD and lower survival [18] or increased incidence of major adverse cardiac events in premenopausal women [19] or a rapid progression of coronary atherosclerosis [20].

Control of AA amyloidosis complicating Crohn's Disease: a clinico-pathological study [21] (Marie A. Denis and René Fiasse)

The conclusions that vigorous treatment including anti-tumour necrosis factor (TNF)-α agents of Crohn's disease (CD) complicated by AA amyloidosis, reduce amyloid A production, were confirmed [22–24]. Long survival after kidney transplantation for end-stage renal disease was also confirmed [24]. However failure of anti-TNF-α therapy of secondary AA-amyloidosis was reported. Courties *et al.* [25] treated 12 patients with rheumatologic diseases associated wit AA amyloidosis, including six non-responding to anti-TNF-α therapy, with tocilizumab (TCZ), a humanized anti-interleukin-6 receptor antagonist. CRP levels decreased in 11 patients and proteinuria in 3. Six out of the eight patients with rheumatoid arthritis were ameliorated, including one non-responder to anti-TNF-α. Lane *et al.* [26] reported that in 20 patients with autoinflammatory diseases and AA amyloidosis treated by TCZ, serum amyloid A significantly fell within 10 days, and amyloid deposits assessed by Serum Amyloid P component (SAP) scintigraphy either regressed or remained stable.

Thymosin β4 protects C57BL/6 mice from bleomycin-induced damage in the lung [27] (Enrico Conte and Maria Iemmolo)

Following our first report showing the Thymosin β4 (Tβ4) protective role in lung toxicity associated with bleomycin (BLEO) treatment in C57BL/6 mice we investigated pertinent mechanisms in CD-1 mice. We published results confirming that bleomycin-induced inflammation and lung damage were significantly reduced by Tβ4 that was also able to substantially inhibit the ongoing BLEO-induced fibrosis at 7 days after intratracheal BLEO delivery [28]. Furthermore, we demonstrated that Tβ4 co-treatment significantly halted the increase in the amount of IL17-producing cells in blood and inhibited IL-17 expression in the lung of BLEO-treated mice. In subse-

quent studies needed to assess its putative antifibrotic properties we showed that despite its protective role in mice treated with bleomycin at 7 days, Tβ4 failed to prevent fibrosis induced by the drug at 14 and 21 days, at variance with its N-terminal fragment Ac-SDKP [29]. We thus suggest that Ac-SDKP may have greater potential as an anti-fibrotic agent in the lung.

Platelet count predicts cardiovascular mortality in very elderly patients with myocardial infarction [30] (Georg Goliasch and Alexander Niessner)

No new evidence for the age-dependent predictive effect of platelet count has accumulated in patients with acute myocardial infarction (AMI). However, in a community based population of 36 262 individuals > 65 years a U-shaped association between platelet count and mortality has been observed with shorter survival with low and high platelet count [31]. With regard to related pathophysiologic mechanisms, new research focused on modified risk predictors related to platelet count. A high platelet-to-lymphocyte ratio predicted all-cause mortality in 639 patients with AMI [32]. Furthermore, the predictive value of immature platelet count has been assessed in 98 patients with coronary artery disease [33]. A high immature platelet count was associated with major adverse cardiovascular events. High platelet mass, another evolving biomarker, was an independent predictor of cardiovascular mortality in 2572 AMI patients [34]. In conclusion the predictive value of parameters related to platelet count is in the centre of ongoing research.

Sfrp5 correlates with insulin resistance and oxidative stress [35] (Maren Carstensen-Kirberg and Christian Herder)

Our results indicated that serum Sfrp5 correlated positively with insulin resistance and markers of oxidative stress but not with inflammatory proteins [35]. In the meantime, we corroborated our findings by showing that Sfrp5 impairs insulin signaling in primary human adipocytes *in vitro* [36]. In contrast, two novel studies failed to demonstrated a positive association between circulating Sfrp5 and HOMA-IR [37,38]. No new data became available regarding the association between Sfrp5 and oxidative stress. Regarding anti-inflammatory properties of Sfrp5 in humans, we found a significant reduction of IL-6 release by Sfrp5 in TNFα-stimulated primary human adipocytes [36]. Two other studies were in line with this observation because they reported that circulating Sfrp5 was associated positively with the anti-inflammatory adiponectin and inversely with the pro-inflammatory cytokines TNFα and IL-1β [37,39]. Further studies are necessary to clarify the potential dual function of Sfrp5 in the regulation of cytokine release and insulin sensitivity.

Nonalcoholic fatty liver in nondiabetic patients with acute coronary syndromes. [40] (Gabriele Cioni and Rosanna Abbate)

In these last 2 years further evidence was collected that non alcoholic fatty liver disease (NAFLD) is associated with clinical and subclinical coronary atherosclerosis [41], mainly evaluated as calcium coronary score, and with high risk coronary plaques independently of the extension and severity of coronary artery disease (CAD) [42]. This association was reported in patients with CAD and in healthy control subjects in different etnias, was stronger in female but not confirmed in menopause [43]. A high incidence of NAFLD was clearly reported in diabetic patients with CAD, related to a worse glycemic metabolic control [44]. The association between NAFLD and CAD was independent of traditional risk factors, of genetic metabolic traits but modulated by low-grade inflammation [45].

Based on unpublished data from our group, a role of NAFLD as independent predictor of extracoronary atherosclerotic burden was shown in healthy control subjects at low cardiovascular risk score. We investigated carotid intima-medial thickness (C-IMT), femoral intima-medial thickness (f-IMT), NAFLD, by ultrasound, and endothelial function, by peripheral-arterial-tonometry, in 220 subjects (male: 100, female: 120; 45·42 ± 13·22 years old); a NAFLD score > 3 selected patients with worse extracoronary atherosclerotic burden independently of traditional risk factors. Evidence that was accumulated in the meanwhile, reinforces the conclusion of our abstract. NAFLD is an independent predictor of subclinical coronary and peripheral atherosclerotic burden also in asymptomatic patients for cardiovascular disease. The study of NAFLD can help in selecting patients at high cardiovascular risk not identified by the evaluation of traditional cardiovascular risk factors according to available score. The understanding of the pathophysiological mechanisms underlying the association between NAFLD and CAD could open new prevention and therapeutic opportunities.

Gender dimorphic increase in Retinol Binding Protein-4 (RBP-4) and Neutrophil Gelatinase-Associated Lipocalin NGAL in children born after IVF: an epigenetic phenomenon? [46] (Sophia D. Sakka and Ioannis Papassotiriou)

Retinol-binding protein 4 (RBP-4) and neutrophil gelatinase-associated lipocalin (NGAL) are early indices of insulin resistance. Since our study was published [46], various studies confirmed the effect of assisted reproduction techniques (ART) on glucose metabolism and insulin resistance. In a prospective study Pontesilli *et al*. [47] found higher glucose levels among children conceived through *in vitro* fertilization (IVF)/intracel-

lular sperm injection (ICSI) compared to children of fertile couples, in the absence of an effect on children of subfertile couples, suggesting that it is the specific ART procedure itself that is responsible for this effect. In another study by Chen *et al.* [48] peripheral insulin sensitivity as measured by the hyperinsulinemic-euglycemic clamp was significantly lower in IVF vs. naturally conceived young adults. Gkourogianni *et al.* [49] performed a metabolomic analysis on girls conceived by ICSI and revealed significantly increased levels on most metabolites related to obesity, insulin resistance and metabolic syndrome, compared to controls, even before they were biochemically evident.

Microbiological screening for earlier detection of central venous catheter–related bloodstream infections [50] (Robert Krause and Jasmin Wagner)

Whereas CRBSI screening performed well in hemodialysis patients by investigating both lumen of a CVC, the sensitivity, specificity, PPV and NPV were lower in haematooncological patients where only one CVC lumen could be sampled [50]. To validate this drawback of sampling only one lumen recently 182 haematooncological patients with 342 catheter periods and 6466 CVC days were analyzed [51]. In this study the sensitivity and specificity of the universal PNA FISH screening were 12% and 98%, the PPV and NPV were 22% and 95%, the sensitivity and specificity of the AOLC screening were 29% and 97%, the PPV and NPV were 33% and 97%, respectively. Additionally low microbial burden in catheter blood causing CRBSI but not detectable by screening PNA FISH and AOLC tests or impossible allocation of CRBSI to a certain CVC lumen due to inadequate labeling of the routine blood samples contributed to screening failures.

Preserved thrombin-inducible platelet activation in thienopyridine-treated patients [52] (Thomas Gremmel)

In a subsequent study, we determined platelet response to agonists specific for protease-activated receptors (PAR)-1 and -4 by multiple electrode impedance aggregometry in 82 patients on stable doses of clopidogrel or prasugrel. We found that PAR responsiveness is preserved in the majority of patients with adequate clopidogrel-mediated inhibition of the platelet P2Y12 receptor, and still in about 20% of those with adequate inhibition by prasugrel [53]. These data reinforce the conclusion of our publication in the European Journal of Clinical Investigation that even patients with adequate thienopyridine-mediated platelet inhibition often show a preserved responsiveness to thrombin. In another publication, we investigated the association of PAR-1-mediated platelet activation with clinical outcomes after angioplasty and stenting for peripheral arterial disease. We showed that high PAR-1-mediated P-selectin expression and glycoprotein IIb/IIIa activation are strong predictors of adverse ischemic events in patients undergoing infrainguinal angioplasty with stent implantation thereby demonstrating the clinical relevance of our previous findings [54].

Androgen activity, ischaemic heart disease and risk factors among men in NHANES III [55] (C Mary Schooling)

Evidence has now accumulated which strengthens the previous conclusion that the androgen biomarker androstanediol glucuronide (3α-diol-G) has associations with cardiovascular disease risk factors similar to those seen in randomized controlled trials, with corresponding implications for raising androgens [55]. The paper showed that in men 3α-diol-G was positively associated with ischemic heart disease and blood pressure; the more commonly used androgen biomarker, serum testosterone, was not [55]. Subsequently, two large well-conducted pharmaco-epidemiology studies showed exogenous testosterone positively associated with myocardial infarction [56,57]; Health Canada and the US Food and Drug Administration issued warnings and required label changes because of the risk of heart attack (and stroke) on testosterone [58,59], Health Canada also warned about testosterone raising blood pressure [59]. The conclusion should now be extended to clarify that endogenous 3α-diol-G is a guide to the effects of exogenous testosterone, endogenous and exogenous androgens may have similar effects and androgens are a new cardiovascular disease risk factor.

Abdominal obesity with hypertriglyceridaemia, lipoprotein(a) and apolipoprotein A-I determine marked cardiometabolic risk [60] (Altan Onat and Günay Can)

A 5-years' prospective Cox regression analysis of about 2200 middle-aged adults categorized to abdominal obesity and hypertriglyceridemia showed a spectrum of excess coronary heart disease (CHD) risk for hypertriglyceridemic waist (HtgW) phenotype, compared to the 'healthy' and hypertriglyceridemic categories combined (unpublished data). This excess risk was further modulated by gender and sex hormone-binding globulin (SHBG) values. SHBG conferred a significant 2·5-fold CHD risk in women when –paradoxically– elevated SHBG levels interacted. SHBG emerged as protective against type-2 diabetes. Adjusted means of lipoprotein[Lp](a) were inverse to apolipoprotein(apo)B-containing lipoproteins in subjects with HtgW compared with those in the 'healthy' category, suggesting the operation of

autoimmune complex involving Lp(a) [61]. HtgW phenotype formed the enhanced proinflammatory state, in which environment SHBG, in addition to harboring protective properties, exhibited a U-shaped risk curve, and acted as a glycoprotein converted inflammatory, analogous to dysfunctional high-density lipoprotein [62,63], apoA-I or apoE [64,65].

Clinical and genetic characteristics of Chinese patients with hereditary haemorrhagic telangiectasia–associated pulmonary hypertension [66] (Xiao-Jian Wang and Zhi-Cheng Jing)

Hereditary hemorrhagic telangiectasia (HHT) is the most common genetic disease of blood vessels and characterized by vast phenotypic variability. Pulmonary arterial hypertension (PAH), which was initially thought to be rare in HHT, has been increasingly recognized as a common and severe complication of HHT [67,68]. Although the underlying cause of HHT has been attributed to a number of mutations within genes in the transforming growth factor-beta (TGF-β), the phenotypic variability of HHT patients could not be solely explained by the genetic defects. Indeed, the absence and presence of PAH were observed in families who carry the same mutation in our study[66]. Therefore, the significant intra-familial variation in phenotype strongly indicates the effect of genetic modifiers on shaping the HHT phenotype and outcome. With the help of whole-genome and whole-exome sequencing, we are planning to elucidate the additional genetic modifiers for PAH in HHT patients.

ProHNPs are the principal α-defensins of human plasma [69] (Andreas Glenthøj and Niels Borregaard)

Our initial study demonstrated that proHNPs are abundant in human plasma and exclusively originate from myeloid precursors in the bone marrow [69]. We speculated that proHNPs in plasma would be a specific marker of bone marrow myelopoiesis. To test this hypothesis in a clinical setting, we obtained daily plasma samples from patients undergoing hematopoietic stem cell transplantation (SCT) or high-dose chemotherapy [70]. In consistence with our theory, proHNPs disappeared from plasma following myeloablation or high-dose chemotherapy and their return preceded reappearance of neutrophils in blood counts. In patients undergoing allogeneic SCT, proHNPs on average rose 6·3 days before neutrophils recurred in peripheral blood counts thus heralding bone marrow engraftment and the end of life-threatning neutropenia. Obviously, this is useful in clinical hematology and we are currently exploring other applications for measurement of proHNPs in plasma.

The relation between body iron stores and adipose tissue function in patients with manifest vascular disease [71] (Jan Westerink and Frank LJ Visseren)

In 2013 we reported in this journal the absence of a relation between plasma ferritin and adiponectin levels in patients with manifest vascular disease [71]. Since then no studies have investigated this relation in this specific and important population. Research in the general population, including some patients with vascular disease, has again proven the inverse relation between plasma ferritin and adiponectin levels and also found a relation with adipose tissue insulin resistance [72,73]. In our report we also showed the proinflammatory effect of free iron on human preadipocytes and absence of such an effect in human differentiated adipocytes. A recent study supports our finding in a murine model (3T3-L1) where stimulation of differentiated adipocytes with FeSO4 does not increase interleukin-6 (IL-6) in the medium. Interestingly, FeSO4 stimulation did have a potentiating effect on LPS induced inflammation which warrants further investigation [74]. Not only iron excess but also iron deficiency has a proinflammatory role in adipocytes, including a detrimental role on adipogenesis, as shown in a recent elegant study [75].

Tropisetron attenuates amyloid-beta-induced inflammatory and apoptotic responses in rats [76] (Gohar Fakhfouri and Kazem Mousavizadeh)

Results of our very recent study indicate that tropisetron can attenuate H2O2-induced neurotoxicity in differentiated PC12 neuron by decreasing the contents of apoptotic proteins caspase 3 and caspase 12 while increasing the levels of anti-inflammatory transcriptional factors Nrf2 and HO-1. Importantly, α7nAChR mediated some neuroroprotective actions of tropisetron in PC12 cells as they were reversed by MLA, a selective α7nAChR antagonist. It is noteworthy that PC12 cells also express 5-HT3 receptors and therefore engagement of these receptors in neuroprotective aspects of tropisetron should not be excluded [77,78]. Corroborating this finding, a recent study has shown that tropisetron suppresses transforming growth factor 1 beta (TGF1β)-induced collagen synthesis independent of 5-HT3 receptor but through α7nAChR [79]. Various mechanisms might contribute to the beneficial effects observed here with tropisetron: [77] decrease in intracellular calcium; [78] inhibition of calcineurin phosphatase activity; [79] acting as a partial agonist on α7nAChR [80].

Symptom patterns can distinguish diverticular disease from irritable bowel syndrome [81] (Rosario Cuomo and Paolo Andreozzi)

In our study, we found that abdominal pain lasting for more than 24 h better discriminates patients with symptomatic uncomplicated diverticular disease (SUDD) from irritable bowel syndrome (IBS) [81]. Recently, Tursi *et al.* [82] have found that, in patients with symptomatic diverticular disease, fecal calprotectin test was positive in 64·3% of patients who referred abdominal pain lasting for at least 24 consecutive hours (long-lasting pain) in left lower abdomen, while no positive test was found in patients without long-lasting pain. This result suggests that symptoms patterns might be helpful to discriminate DD patients with concurrent IBS from patients where symptoms are related to the presence of diverticula.

Interestingly, a recent study of Yamada *et al.* [83] has demonstrated that the location of diverticula is strictly related to IBS-like symptoms development: patients with left-sided and bilateral diverticulosis were three times more likely to have IBS-like symptoms than those with right-sided lesions. This study showed that the left location of diverticula seems to be a key factor in the pathogenesis of IBS symptoms in DD patients.

Adiponectin, visfatin and regional fat depots in normal weight obese premenopausal women [84] (Tomasz Miazgowski, Paweł Sołtysiak, and Bartosz Miazgowski)

Our results have been reinforced by new findings that normal weight obese (NWO) are at risk of abnormal lipid profiles, insulin resistance, hypertension, and metabolic syndrome [85]. Moreover, recent studies have demonstrated that NWO subjects carry a higher subclinical inflammation [86] as well as a higher incidence of subclinical atherosclerosis and number of soft plaque in coronary arteries [87], and increased aortic stiffness [88]. These abnormalities are largely driven by the amount of visceral fat but not body fat [87]. In addition, we have found that even in lean healthy females [89] and males (unpublished data), visceral fat evaluated by a new DXA-derived method show better correlation with unfavorable lipid profile and insulin resistance than android fat. Therefore, many individuals prone to cardiometabolic diseases appear to show, for a giving weight, a greater propensity to accumulate visceral fat, regardless if they are lean, overweight, obese, or normal weight obese.

Long-term survival in elderly patients with stable coronary disease [90] (Martín Ruiz Ortiz and Cristina Ogayar Luque)

In the last 2 years, new observational studies have been published regarding prognosis of stable coronary artery disease in general population [91–95]. These studies have confirmed the ability of simple clinical variables in predicting survival of these patients, as age, sex, smoking, hypertension, diabetes, lipids, heart failure, peripheral arterial disease, atrial fibrillation, stroke, chronic kidney disease, chronic pulmonary disease, liver disease, cancer, depression, anxiety, the absence of previous coronary revascularization, a low ejection fraction, absence of statin treatment, heart rate, creatinine, white cell count, and haemoglobin. However, no new evidence has been published in the specific subset of patients aged 75 years or older (we have not even found any subgroup analysis in the general series recently published addressing this issue), in which, as far as we know, our study is the only one reporting long term survival of this population; so, further investigation is warranted in this field.

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Appendix

Statements made in the Conclusions of the Abstract of original articles published by the European Journal of Clinical Investigation in 2013 and current status for each statement as judged by the authors of each original study

		Current status for the statement				
References	**Statements made in 2013**	**Reinforced n = 23**	**Modified n = 1**	**Weakened n = 0**	**No new evidence n = 3**	**Other n = 1**
[1]	Unlike in younger subjects, in subjects ≥ 50 years old, comorbidities do not mask an effect of OSA on mortality. Among OSA subjects ≥ 50 years old, comorbidities could separate those who may expect an improvement in survival with CPAP treatment from those who may not. Possibly, after the age of 50, OSA per se does not affect survival, but worsens prognosis of subjects with coexisting diseases.	X				
[6]	The discovery of this new albumin gene mutation, probably inherited from a common ancestor, sheds light on the molecular mechanism underlying the analbuminemic trait and may serve in the development of a rapid genetic test for the identification of asymptomatic heterozygous carriers in the Druze population in the Galilee.	X				
[10]	We report for the first time the direct relations of VAI with adipose tissue secretion.	X				
[10]	We report for the first time the direct relations of VAI with functional glycaemic disorders.	X				
[10]	Because VAI is estimated easily with data obtained in everyday practice, it could be used as an indirect index of adiponectin levels and the risk of impaired glucose metabolism.	X				
[15]	Uric acid predicted an increased risk of cardiac mortality across all subgroups of patients with cardiovascular disease. The association between uric acid and cardiac or all-cause mortality had a 'J-shaped' pattern with lowest risk of death in patients with uric acid levels between 5·17 and < 6·76 mg/dL.	X				
[21]	Suppression of Crohn's disease inflammation potentially leads to the control of amyloid A production, assessed by a decrease of serum amyloid A.	X				
[21]	Kidney transplantation provides a long survival.	X				
[27]	This is the first report that shows a Thymosin β4 protective role in lung toxicity associated with bleomycin in a mouse model.	X				
[27]	Future studies are needed to assess its putative antifibrotic properties.		X			
[30]	Our study demonstrates an independent association between elevated platelet count and long-term cardiovascular mortality in the growing and vulnerable group of very elderly acute myocardial infarction patients.				X	

Appendix *Continued*

References	Statements made in 2013	Current status for the statement				
		Reinforced n = 23	Modified n = 1	Weakened n = 0	No new evidence n = 3	Other n = 1
[30]	Nevertheless, the pathophysiologic mechanisms underlying this age-dependent effect have to be further clarified.	X				
[35]	In contrast to obese mouse models, serum Sfrp5 was directly related to HOMA-IR and oxidative stress in humans, but not with apolipoproteins, and thus, associations differed from those found for circulating adiponectin.	X				
[40]	In non-diabetic patients admitted for STEMI NAFLD prevalence was very high.	X				
[40]	Severe NAFLD independently increased the risk for multi-vessel CAD associated to cardiovascular events.	X				
[46]	In our study, IVF children had significantly higher RBP-4 and NGAL levels than controls, suggesting early metabolic derangements that could be attributed to an epigenetic phenomenon.	X				
[46]	Further prospective studies in IVF children will determine the natural course of their metabolic profile.	X				
[50]	The proactive anticipative strategy using microscopic examination of CVC blood samples to anticipate CRBSI in an earlier stage compared with routine measures is a new diagnostic approach in patients with CVCs and a high risk of developing CRBSI.	X				
[52]	Thienopyridine nonresponders are more susceptible to thrombin- and ADP-inducible platelet activation than patients with good platelet inhibition. However, even patients with adequate thienopyridine-mediated platelet inhibition often show a preserved responsiveness to thrombin. These patients may benefit from additional thrombin receptor blockage or inhibition of thrombin generation.					X*
[55]	Androgen biomarkers had inconsistent associations with cardiovascular disease risk factors and ischaemic heart disease. Androstanediol glucuronide, rather than serum testosterone, had associations with cardiovascular disease risk factors more similar to those seen in randomized controlled trials of testosterone therapy, with corresponding implications for raising androgens.	X				
[60]	HtgW is associated with excess inflammatory markers, is predicted in women paradoxically by lower circulating Lp(a) and is associated in both sexes with marked excess cardiometabolic risk to which high apoA-I/HDL-C ratio contributes additively. These findings are consistent in women with apoA-I being oxidized via aggregation to Lp(a).	X				

Appendix *Continued*

References	Statements made in 2013	Current status for the statement				
		Reinforced n = 23	Modified n = 1	Weakened n = 0	No new evidence n = 3	Other n = 1
[66]	Our findings have revealed the clinical phenotype and molecular genetic features of HHT-associated PH in Chinese Han patients and indicate that mutations of ACVRL-1 and ENG are genetic predisposing factors in Chinese patients. Our data further addressed clinical management and have provided limited experience in treating this group of disorders.	X				
[69]	Most HNPs in plasma are in fact proHNPs, which is important given the differences in their origin and biological activities.	X				
[71]	In patients with vascular disease, there is no association between plasma ferritin and adiponectin levels. *In vitro*, free iron induces an inflammatory response in pre-adipocytes, but not in adipocytes. This response was blocked by co-incubation with iron chelators or radical scavengers. Adiponectin secretion by adipocytes was not influenced by free iron.	X[†]			X[‡]	
[76]	Our findings indicate that tropisetron protects against Aβ-induced neurotoxicity *in vivo* through both 5-HT3 receptor-dependent and independent pathways.	X				
[81]	Abdominal pain lasting for more than 24 h discriminates patients with DD compared with those with IBS. Identifying this symptom could be an appropriate strategy to define the diagnosis and management.					
[84]	Compared with healthy controls, women with NWO had higher DBP, TG, LDL, and regional fat and lower HDL. These findings seem to be associated more with excess Android fat than excess %BF.					
[90]	In this study, 4-years overall mortality was 23% among elderly patients with sCAD. Simple clinical variables can identify patients at higher risk of mortality.	X[†]			X[‡]	

ADP, adenosine diphosphate; ACVRL-1, activin receptor-like kinase-1; Aβ, beta-amyloid; BF, body fat; OSA, obstructive sleep apnoea; CVC, central venous catheter; CPAP, continuous positive airway pressure; CRBSI, catheter-related bloodstream infections; DD, diverticular disease; DBP, diastolic blood pressure; ENG, endoglin; HtgW, 'hypertriglyceridemic waist' phenotype; HDL, high-density lipoproteins; LDL, low-density lipoproteins; HNPs, human neutrophil peptides; HHT, hereditary haemorrhagic telangiectasia; IBS, irritable bowel syndrome; Lp(a), lipoprotein(a); VAI, visceral adiposity index; STEMI, ST Elevation Myocardial Infarction; sCAD, stable coronary artery disease; PH, pulmonary hypertension; NAFLD, non alcoholic fatty liver disease; CAD, coronary artery disease; IVF, *In Vitro* fertilization; RBP-4, retinol-binding protein 4; NGAL, neutrophil gelatinase-associated lipocalin; NOW, normal weight obesity; TG, triglycerides.
*PAR-1-mediated platelet activation is associated with clinical outcomes following peripheral angioplasty and stenting for lower extremity artery disease.
[†]Iron and (pre)adipocytes [71]; Simple clinical variables can identify patients at higher risk of mortality [90].
[‡]Ferritin/adiponectin in vascular disease [71]; In this study, 4-years overall mortality was 23% among elderly patients with sCAD [90].

