CARDIOVASCULAR RISK MANAGEMENT:

APPLYING THE LATEST INSIGHTS TO CLINICAL CARE IN RUSSIA

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In Moscow on October 14-15, 2016, physicians and experts gathered for a Cardiovascular Risk Master Class, to learn and update how the latest scientific insights can be applied to clinical care. The recent data on the pathophysiology of coronary artery disease and stroke were discussed, including how intensive treatment of dyslipidaemia and hypertension can prevent cardiovascular events in high-risk populations.
This Master Class aimed to provide a platform for the review, exchange and assimilation and implementation of important data and ideas, in order to accelerate the translation of the latest insights in to clinical practice in Russia. By considering Russian epidemiology and guidelines on diagnosis and treatment, it can be concluded where management of Russian patients could improve. This document captures the essentials of what was discussed and what is to be implemented in routine clinical practice in Russia.

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Introduction on CV risk management

Cardiovascular disease (CVD) accounts for 17.3 million deaths worldwide on an annual basis, 4 million of which are counted in Europe (1, 2). In Europe, it was estimated that in 2012 47% of deaths were attributed to CVD (2), allowing a large opportunity to lower CV risk in the population and thereby reduce deaths.

Managing lifetime risk, as opposed to 5- or 10-year risk, is an emerging concept in modern CV risk management. This approach is also referred to as 'investing in your arteries', in an attempt to emphasise that there is huge unmet opportunity for intervention in the preclinical stage, i.e. primary prevention of CVD burden. Throughout life, CVD risk should be managed by addressing multiple risk factors. Multiple studies have shown that a broader risk management approach controlling multiple risk factors and starting early pays off in terms of clinical benefit. It is worth noting that arterial disease has been detected in people who died at young age (even younger than 20 years) due to non-cardiac reasons (3). Improvement of risk factors early in life should not only yield clinical benefit for the individual, but is also more cost-effective for healthcare systems.

This document aims to explore opportunities to improve CVD prevention and CV risk management. Risk assessment strategies, preventive and therapeutic interventions to lower CV risk factors are discussed, considering what international and Russian national guidelines recommend. Epidemiology of risk factors in Russia and the current status of Russian CV risk factor management is outlined, from which opportunities arise to improve care of CVD patients. Final thoughts focus on which steps may be taken to reduce the burden of CV disease in Russia.

Risk assessment, and communicating risk to maximise prevention

To benefit from prevention opportunities, it is important to assess and communicate the CVD risks. This is not always straightforward. For instance, the 10-year risk cut-off is somewhat arbitrary. Also, the SCORE risk assessment chart disenfranchises young people, in particular women (4). It has been described that 56% of American adults have low (<10%) 10-year risk, but high lifetime (>39%) risk (5). Thus, better risk stratification in the lower absolute risk groups is warranted. It is also important to apply recent algorithms and re-classification models apart from SCORE, such as QRISK, JBS3 and Pooled Cohort Equation (ACC/AHA Guidelines 2013).

In particular, in the United Kingdom, a different approach is followed, as described in the JBS3 guidelines (and see www.jbs3risk.com). Instead of 10-year risk, heart age is considered; which not only gives an indication of whether one's heart is in good shape relative to one's biological age but the calculator also shows the effect of modifying risk factors. Showing these effects graphically can greatly motivate patients to improve CV risk factors (6).

For some individuals, simple principles of risk assessment may suffice; it might not be needed to apply formal methods. Persons with documented CVD, type 1 or type 2 diabetes (T2DM), very high level of individual risk factors, and/or chronic kidney disease (CKD), are automatically considered to be at very high CV risk (7).

The European CV risk management (CVRM) guidelines acknowledge socio-economic status/social isolation/lack of social support, family history of premature CVD, body mass index (BMI) and central obesity, CT coronary calcium score, atherosclerotic plaques determined by carotid artery scanning and the ankle-brachial BP index as risk modifiers that may reclassify individuals to a higher risk category. Routine assessment of circulating or urinary biomarkers is not recommended for refinement of CVD risk stratification (4).

Preventive measures should be aimed at the young, even in children, and should involve innovative digital health technology, which could empower individuals to be fit or otherwise improve lifestyle.

Thinking beyond the heart, improving vascular risk factors likely also has a positive impact on the brain, as evidence suggest that CV risk factors in midlife increase the risk of dementia (8). The FINGER trial results suggest that intervention can favourably affect the risk of cognitive decline (9).

Various methods to detect atherosclerosis exist, with different advantages and disadvantages. The options include cheap indirect arterial stiffness/functional tests that allow risk stratification and assessing prognosis, but that may detect a disease process at a too early stage that would not have come into play if undetected, as well as invasive methods that have fair accuracy, but might come with complications. Recent EAS/EAS Guidelines (2016) do not recommend using intima media thickness (IMT), but allow the use of coronary calcium score and carotid plaques as a re-classification tool in patients with low and intermediate CVD risk (10).

Novel non-invasive methods are being developed to assess very early atherosclerotic lesions, for example high-resolution B-mode ultrasound imaging of the common carotid artery structure and its pulse-motion (M-mode).

Prevention of ischemic stroke deserves specific attention, as outcome in survivors of stroke is often poor. Moreover, secondary prevention in stroke patients is of utmost importance, as stroke recurrences account for 15-20% of all stroke. Residual problems, including functional disabilities and dependences, and cognitive or depressive symptoms are common. A study that followed almost 2500 Dutch patients with transient ischaemic attack (TIA) or minor ischemic stroke for a mean of 10.1 years, described that 60% died and 54% had at least one vascular event. The 10-year risk of death was 42.7% (11).

Stroke is largely preventable, and hypertension is the most important risk factor for ischemic stroke, according to the INTERSTROKE study (12). Randomised controlled studies have demonstrated that both blood pressure (BP-) and LDL-lowering can be employed to lower stroke risk. The ACCORD BP trial compared the effect of intensive (<120 mmHg) or standard (<140 mmHg) BP lowering therapy in patients with T2DM, followed for 4.7 years, on the primary outcome of nonfatal myocardial infarction (MI), nonfatal stroke and CV death (13). More adverse events (AEs) attributed to BP therapy, such as dizziness, syncope, hyperkalaemia and hypokalaemia, were reported in the aggressively treated group and these patients had a lower estimated glomerular filtration rate (eGFR) at the end of the study. No difference between the treatment groups was seen in the composite primary outcome. When looking at the components of the primary outcome, the incidence of non-fatal stroke was significantly lower in the intensive treatment arm (13).

The SPRINT trial also compared an intensive (<120 mmHg) with a standard (<140 mmHg) BP-lowering treatment strategy, on the primary composite outcome of MI, other acute coronary syndrome (ACS), stroke, heart failure (HF) and CV death. The trial stopped early after 3.26 years because of benefit in the intensive treatment group (14). A reduction of 25% in the primary composite endpoint was observed with intensive treatment, and total mortality was reduced by 27%. As for secondary outcomes, MI, ACS and stroke did not show a difference between treatment groups. Significantly higher rates of some AEs were observed in the intensive-treatment group (14). In an analysis on outcome data of the ACCORD and SPRINT trials, reduced risk of stroke and HF were seen based on the combined data (15).

The ASCOT-LLA trial included high-risk patients but without a history of coronary heart disease (CHD) with untreated (SBP>160 mmHg and/or DBP >100 mmHg) or treated (SBP>140 mmHg and/or DBP> 90 mmHg) hypertension. Patients in the lipid-lowering arm were eligible if they also had total cholesterol <6.5 mmol/L and were not taking a statin or a fibrate (16). After a year, total cholesterol and LDL-c were lowered by 1.3 and 1.2 mmol/L respectively, in those treated with atorvastatin 10 mg, as compared with placebo. By the end of the trial, at around 3 years, the treatment effects had reduced to 1.1 and 1.0 mmol/L, respectively. Atorvastatin therapy yielded a reduction of 36% of the primary endpoint of non-fatal MI and fatal CHD, as compared with placebo therapy. The secondary endpoint of fatal and non-fatal stroke was reduced by 27% (16).

The SPARCL study was the first double-blind, randomised, placebo-controlled trial to evaluate prospectively the effect of intensive (statin treatment) in prevention of recurrent stroke as a primary end point (17). Over a study period of 6 years, 16% risk reduction of fatal or non-fatal stroke was seen with atorvastatin as compared with placebo (Adjusted HR: 0.84, 95%CI: 0.71-0.99, P=0.03). The secondary endpoint of time to major coronary event showed a risk reduction of 35% with atorvastatin (17). A study showed an increased benefit in reducing stroke risk when having an increasing number of the following parameters: LDL-c <70 mg/dL, BP <120/80 mmHg, triglycerides (TG) <150 mg/dL and HDL-c >50 mg/dL (18), with an HR of 0.354 (95%CI: 0.130- 0.963, P=0.042) when all 4 parameters are met. Similarly risk of major CV events was reduced down to an HR of 0.247 (95%CI: 0.091 – 0.669, P=0.0059) when all 4 parameters were met (18). Secondary analysis of the SPARCL study revealed that excess in haemorrhagic stroke is mainly related to inappropriate control of BP rather than intensive lipid-lowering therapy (OR 6.19 [95%CI: 1.47-2.61], p< 0.01) (19).

The HOPE-3 trial evaluated the effects of BP-lowering treatment with a fixed dose combination of candesartan 16 mg and HCTZ 12.5 daily, or initial dose of rosuvastatin 10 mg daily, or combined BP- and cholesterol-lowering, in an intermediate risk population without CVD. In the BP-lowering arm, no significant effect was seen on the endpoint of CV death, MI, stroke, cardiac arrest, revascularisation and HF (HR: 0.95, 95%CI: 0.81-1.11, P=0.51). When looking at prespecified subgroups based on thirds of SBP, only those with SBP >143.5 mmHg showed a benefit of treatment with candesartan plus HCTZ as compared with placebo (HR: 0.76, 95%CI: 0.60-0.96). Participants treated with rosuvastatin did show a reduction of the combined endpoint, as compared with placebo (HR: 0.75, 95%CI: 0.64-0.88, P=0.0004). Incidence of coronary heart disease (HR: 0.75, 95%CI: 0.58-0.96, P=0.0214) and stroke (HR: 0.70, 95%CI: 0.52-0.95, P=0.0227) were also reduced in those treated with rosuvastatin as compared with placebo (16).

A systematic review and meta-analysis of all randomised trials testing statin drugs published before August 2003 that evaluated the relationship between LDL-c lowering and reduction in risk of stroke revealed that each 10% decrease of LDL-c lowers stroke risk by an estimated 15.6% (95%ci: 6.7%-23.6%, R=0.58, P=0.002)(20).

In summary, while the ACCORD trial showed that lowering BP aggressively in diabetics did not reduce CV events (except stroke), but increased serious adverse effects, the SPRINT data suggested that lowering BP aggressively did reduce CV events in non-diabetics. The ASCOT-LLA data revealed that lowering LDL-c with atorvastatin in hypertensive patients who also have other risk factors, lowered CV events and stroke. The HOPE-3 study showed that lowering LDL-c with rosuvastatin reduced CV events in patients at intermediate risk; BP lowering was only effective in the highest BP tertile. Finally, SPARCL showed that lowering LDL-c with atorvastatin 80 mg reduced cerebrovascular and coronary events in patients with stroke or TIA.

Addressing risk factors to reduce CV risk

Lipid-lowering to reduce CV risk

Treating to lower LDL-c levels with statins is an effective modality to reduce CV risk (21). In 2005, the cholesterol treatment trialist (CTT) Collaborators published the now well-known graph showing the relation between the proportional reduction in major vascular events and mean absolute LDL-c reduction. Plotting observations of fourteen statin trials in one graph suggests a linear association, which has often been summarised as 'the lower the LDL-c, the better'. An updated figure based on meta-analyses of different levels of achieved LDL-c in a total of 27 trials has now been published. The same publication reports that the same clinical benefit of statin therapy is seen in many different subgroups of patients, with an overall effect in all patients (n=24957) of RR: 0.79 (95%CI: 0.77-0.81), at an annual event rate of 4.0% per year in the control arm (21). Moreover, the event reduction is independent of baseline LDL-c level (22).

When stratifying according to baseline risk, a consistent risk reduction is seen in patients with >10% major vascular event risk onwards. In those in the lowest two categories (<5% and between 5 and 10% risk), the risk reduction achieved with statin therapy per 1 mmol/L reduction in LDL-c may be even larger (RR: 0.62, 95%CI: 0.47-0.81 and RR: 0.69, 95%CI: 0.60-0.79 respectively). It is considered that relative risk reduction is independent of baseline risk.

A 3-dimensional graph in a recent paper by Collins et al. in the Lancet (21) illustrates that the number of predicted absolute avoided CV events (after the first year) increases with increasing LDL-c reduction achieved with statin therapy, as well as with increasing 5-year risk of major vascular events. The two variables strengthen each other's effect, up to 1440 predicted CV events avoided in 10 000 patients, with an >30% 5-year risk of major vascular events who had 2.0 mmol/L LDL-c reduction on statin therapy. The relative treatment benefit increases with the duration of statin therapy, with RR: 0.76 (95%CI: 0.74-0.79) per 1 mmol/L LDL-c lowering seen for years 1 to >5 years of treatment, as compared with RR: 0.91 (95%CI: 0.85-0.97) in the first year of statin therapy (21).

Statin therapy specifically lowers vascular mortality (RR:0.88, 95%CI: 0.84-0.91 per 1 mmol/L in LDL-c reduction), with the largest effect on coronary causes (RR: 0.80, 95%CI: 0.74-0.87). It does not significantly affect non-vascular causes of mortality (RR: 0.96, 95%CI: 0.92-1.01), including cancer (RR: 0.99, 95%CI: 0.91-1.09). An analysis of the effect of LDL-c lowering with statins on cancer incidence shows no effect on any cancer (RR: 1.00, 95%CI: 0.96-1.04), nor on any subtype (21).

Evidence now suggests that achieving even very low LDL-c levels with statins is safe and associated with low event rates (23). Genetic evidence confirms this observation, as subjects with a specific variant in the proprotein convertase subtilisin/kexin type 9 (PCSK9) gene that caused them to be exposed to low LDL-c levels from birth onwards, are very rarely affected by CHD (24).

The HOPE-3 trial filled a data gap on different ethnicities by including 20% white Caucasians, 28% Latin Americans, 29% Chinese, 20% other Asians and 2% black Africans. The trial reported a 25% reduction with rosuvastatin therapy in CV death, MI, stroke, cardiac arrest, revascularization and HF (HR: 0.75, 95%CI: 0.64-0.88, P=0.0004), as compared to placebo over up to 7 years of follow-up (25).

The benefits of LDL-c lowering have now been shown to last after the intervention: long-term follow-up of the West of Scotland Coronary Prevention Study (WOSCOPS)(26), finished in 1995, showed that the clinical benefit of statin therapy as primary prevention in men (45-64 years old) with high LDL-c (mean 192 mg/dL, 5.0 mmol/L) at baseline extended beyond the treatment period. At the end of the actual study period (average 4.9 years of follow-up), pravastatin 40 mg daily treatment was associated with a reduction of the primary endpoint of CHD death plus non-fatal MI by 31% (95%CI: 17-43%). Linkage to electronic health records allowed further follow-up, and major incident events were analysed in the next 15 years. Post-trial statin use was recorded 5 years after the trial, but not in the last 10 years. After a total of 20 years of follow-up, men allocated to pravastatin had reduced all-cause mortality (HR: 0.87, 95%CI: 0.80-0.94, P=0.0007), which was mainly attributable to lower CV deaths (HR: 0.79, 95%CI: 0.69-0.90, P=0.0004). This lasting benefit on survival and CV morbidity after 5 years of statin treatment has been called the legacy effect of statin therapy (27).

Multiple trials confirm the benefit of lifetime lowering of LDL-c, either due to genetic variants or due to pharmacological interventions (28). A recent meta regression analysis of concluded that statin and non-statin therapies (diet, bile acid sequestrants, ileal bypass or ezetimibe) that act predominantly via upregulation of LDL-receptor expression to reduce LDL-c were associated with similar RRs of major vascular events per change in LDL-c (23% relative risk reduction per 1 mmol/L (38.7 mg/dL) reduction. Levels of achieved LDL-c were lower after these treatments, and so were rates of major coronary events (RR: 0.77, 95%CI: 0.75-0.79, P<0.001) (4).

For other interventions, the observed RRs vs the expected RRs based on the degree of LDL-C reduction in the trials were lower than expected for fibrates (ie, greater risk reduction), higher than expected for cholesteryl ester transfer protein (CETP) inhibitors, and nonsignificantly higher for niacins and nonsignificantly lower for PCSK9 inhibitors (4).

Genetic evidence on the benefit of long term favourable risk profile also stems from a large study on over 100 000

subjects, which used an LDL-c genetic score and a systolic blood pressure (SBP) genetic score based on 46 and 33 polymorphisms respectively (29). The study aimed to assess the impact of long-term exposure to these favourable genetic polymorphisms, and indeed found a lower odds of CV events with a low (below median) LDL-c genetic scores (OR: 0.758, 95%CI: 0.715-0.804), a low SBP genetic score (OR: 0.821, 95%CI: 0.779-0.865) and an even stronger effect when both genetic scores were below the median (OR: 0.542, 95%CI: 0.509-0.577). Thus, it was concluded that these risk factors have an independent, multiplicative and cumulative causal effect on CV events (29). Hence, even modestly lowering both risk factors for a considerable period of time has a substantial effect on lifetime risk of CV events. The findings suggest that CV events are largely preventable with simple prevention programmes promoting long-term exposure to lower LDL-c and SBP, beginning in early adulthood (after 40 years).

Lipid-modifying therapy beyond statins

Individual responses to statins are highly variable (23) and the response to statins affects CV risk reduction (30). Discontinuation of statin therapy is, especially in high-risk CVD patients a problem, as it is associated with increased risk of MI (31). Unfortunately, early statin discontinuation is affected by negative statin-related news stories (31).

In those unable to reach sufficient LDL-c lowering on statins, or those intolerant to statin therapy, other lipid-modifying treatments may be employed, some of which are discussed below.

Ezetimibe is a cholesterol absorption inhibitor, often used as add-on therapy mostly in FH patients or in those patients who do not achieve LDL-c on maximal statin therapy.. In the IMPROVE-IT study (32) it reduced the primary endpoint of CV death, MI, unstable angina requiring hospitalisation, coronary vascularisation (>30 days) or stroke in patients with ACS (HR: 0.936, 95%CI: 0.89-0.95, P=0.006) over a period of 7 years (event rate with simvastatin: 34.7% at mean LDL-c at 1 year of 69.9 mg/dL or ˜1,8 mmol/L, and with simvastatin plus ezetimibe: 32.7%, mean LDL-c at 1 year: 53.2 mg/dL or ˜1.4 mmol/L, translating into a number needed to treat of 50). Subgroup analyses showed no benefit in non-diabetics (73% of the population, HR: 0.98, 95%CI: 0.91-1.04, P=0.49, diabetics: HR: 0.86, 95%CI: 0.78-094, P=0.001), nor in patients younger than 75 years old (84% of the population, HR: 0.97, 0.91-1.03, P=0.34, patients >75 years: HR: 0.80, 95%CI: 0.70-0.90, P=0.0003) (32). The effect of ezetimibe as seen in the IMPROVE-IT trial fits on the CTT Collaborators line.

With regard to other non-statin lipid-lowering agents, no benefit has been seen with fenofibrate in patients with diabetes to reduce cardiac death and MI (Field trial (33)) and stroke (added to simvastatin in the ACCORD lipid trial (34). Similarly, niacin added to simvastatin therapy did not provide benefit to high-risk patients in the AIM-HIGH (35) and HPS2-THRIVE (36) trials. International guidelines (2013 ACC/AHA, NICE 2014, ADA) also concluded that there is no data to support the routine use of non-statin drugs to further reduce ASCVD events, but it should be noted that these guidelines were published before IMPROVE-IT.

The 2016 ESC Guidelines state that selective cholesterol absorption inhibitors such as ezetimibe are not usually used as monotherapy to decrease LDL-C concentrations, unless patients are intolerant to statins. They are recommended as combination therapy with statins in selected CVD patients when treatment goal is not attained with the maximal tolerated dose of a statin. A statin combined with ezetimibe is the only combination treatment that has evidence of clinical benefit (one large RCT). Based on the relatively limited body of evidence, the ESC guidelines note that clinicians may restrict the use of this combination to patients at high or very-high CVD risk (7).

Moreover, trials with CETP inhibitors show that not all improvement of lipid levels translates into fewer CV events. Evacetrapib, for instance, in the ACCELERATE trial, was associated with a 130% increase in HDL-c (104 vs. 46 mg/dL) and a 37% reduction of LDL-c (55 vs. 84 mg/dL) in high-risk coronary patients, but no difference was seen in the primary endpoint of CV death, MI, stroke, coronary revascularisation or hospitalisation for angina (event rates 12.8% vs. 12.7% with placebo, HR: 1.01, 95%CI: 0.91-1.12)(unpublished data presented at AHA 2016).

The new PCSK9 inhibitors (evolocumab and alirocumab) now receive attention as lipid-lowering therapy. PCSK9 normally reduces LDL-receptor (LDLR), thereby increasing plasma LDL-c. Inhibiting PCSK9 function stimulates recycling of the LDLR, thereby lowering plasma LDL-c (37). Antibodies directed against PCSK9 have been developed and upon subcutaneous administration, a rapid decline of PCSK9 protein levels is observed, which lasts about 2 weeks. After this, the antibody disappears from the plasma, and as a consequence PCSK9 protein is produced again. Importantly, LDL-c concentration also drops rapidly after the injection, and levels increase again when PCSK9 protein reappears.

In the OSLER-1 and -2 trials, treatment with the PCSK9-antibody evolocumab on top of standard therapy yielded a 45% reduction in LDL-c at 4.5 weeks absolute reduction: 60.4 mg/dL), and about 60% at 12 weeks, which lasted during 48 weeks of treatment. The first observations on the effect of CV events show a reduction (HR: 0.47, 95%CI: 0.28-0.78, P=0.003) with evolocumab as compared with standard therapy in the first year (38). Similar LDL-c reductions have been observed up to 78 weeks with treatment with another PCSK9 antibody alirocumab vs. placebo on top of statin therapy in the ODYSSEY long-term trial. In this trial, a significantly lower rate of MI was seen with alirocumab

(14/1550 events, 0.9%) than with placebo (18/788, 2.3%, P=0.01) (39).

Importantly, no increase in AEs has been observed at very low LDL-c levels that are reached in some patients treated with PCSK9 antibodies. In those reaching LDL-c<25 mg/dL, no increases of serious AEs, muscle-related AEs, creatinine kinase elevations, ALT or AST elevations or neurocognitive events were noted, with treatment with evolocumab or alirocumab (38, 39).

Interestingly, in the imaging study GLAGLOV, monthly treatment with evolocumab on top of statins showed 1% decrease in percent atheroma volume (PAV) as compared with placebo. Normalised total atheroma volume (TAV) decreased by 5.8 mm3 with evolocumab, as compared with 0.9 mm3 on placebo. A greater proportion of patients treated with evolocumab showed plaque regression than in the placebo group (64.3% vs. 47.3%, P<0.001 for PAV and 61.5% vs. 48.9%, P<0.001 for TAV) (40). The observation that not all patients showed regression despite efficient lipid-lowering with PCSK9 inhibition on top of statins, suggests that not all atherogenesis can be explained by LDL-c. Clinical utility of the GLAGOV data is of further discussion, since intensive statin treatment (REVERSAL, ASTEROID, SATURN) yields almost the same benefit, at lower cost.

Recent data from the FOURIER Trial showed additional CVD risk reduction in very-high risk patients who underwent intensive LDL-c lowering with statins and/or ezetimibe and the fully human monoclonal antibody directed to PCSK9, evolocumab (41). The FOURIER trial was a randomised, double-blind, placebo-controlled trial of the PCSK9 inhibitor evolocumab, in 27564 high-risk, stable patients with established CV disease on high or moderate intensity statin therapy, with or without ezetimibe. In the FOURIER study, patients had LDL-c >70 mg/dL (median: 92 mg/dL, IQR: 80-109) and non-HDL-c >100 mg/dL at baseline. Median follow-up was 26 months (IQR: 22-30). 2907 patients experienced a primary endpoint (CV death, MI, stroke, hospitalisation for unstable angina, or coronary revascularisation) and 1829 experienced a key secondary endpoint (CV death, MI or stroke). 69% of participants were on high-intensity statin, 30% on moderate-intensity statin, and 5% used ezetimibe. This is the first study that demonstrated CVD benefit and safety of additional LDL-C reduction to LDL-c levels as low as 30 mg/dl (12). The FOURIER trial results support safety of intensive LDL-c reduction for the risk of diabetes mellitus, neurocognitive function and cancer.

Investigational approaches to lower PCSK9 include vaccines and adnectins, which bind PCSK9 in plasma, or siRNA and small molecules that inhibit PCSK9 synthesis. In the ORION-1 study, first results of an siRNA directed against PCSK9 showed that an injection of inclisiran reduced PCSK9 level effectively, and LDL-c level was reduced up to a least-square mean reduction of about 50% from baseline. Reductions in the levels of PCSK9 and LDL-c were maintained for three months after a single injection. Higher or repeated doses prolonged the reduced levels. No adverse effects were seen in the phase I trial (42). A large multicenter trial evaluating the effect of inclisiran on hard endpoints is planned to investigate if this new treatment will reduce CVD mortality, similar to what was seen in the FOURIER trial.

Blood pressure lowering to reduce CV risk

About 1 in 6 persons are estimated to have hypertension worldwide. Untreated hypertension comes with a high complication rate, with the hazard increasing with higher BP (43). Studies comparing various treatment regimens suggest that the magnitude of BP-lowering linearly correlates with risk reduction of both stroke and CHD (44). The relationship between usual systolic BP (SBP) or diastolic BP (DBP) and ischemic heart disease (IHD) mortality rate shows a steeper linear curve in lower age groups, suggesting that more effect can be obtained when treating early (45).
Optimal BP management largely follows the same principle as lipid management, in the sense that lower BP and an earlier and broader therapeutic approach yields more CV benefit. Long-term follow-up (36 years) of participants of the Framingham Heart Study clearly showed that hypertension contributes to the development of CVD, as biennial age-adjusted rate of CAD, stroke, peripheral artery disease (PAD) and cardiac failure were all higher in those with hypertension, as compared to normotensives. This was true for both men and women.

To diagnose hypertension, ambulatory BP measurement (ABPM) is a better predictor of clinical outcomes than BP measured in the office (46). Specificity and sensitivity are better with ABPM as compared with office and home BP measurement, and when uncertainty exists about the diagnosis, ABPM is the reference standard. Using ABPM avoids treatment in people who are not truly hypertensive, but who show 'white coat hypertension' during clinic measurement. Implementation of ABPM for diagnosis of hypertension was cost effective in England and Wales, as shown by a NICE calculation in which treatment costs were decreased, amounting to a favourable net resource impact *(http://guidance.nice.org.uk/CG127).*

The reverse situation of 'white coat hypertension' is masked untreated hypertension, when patients with apparently controlled hypertension (<140/90 mmHg) during office measurement, have elevated ABPM values over 24 hours (47). This is a problem, as masked hypertension has been associated with poor prognosis (48). BP is variable over the course of a 24 hour period, and some aspects of the variable pattern have been associated with clinical outcomes (49). Visit-to-visit variability in SBP and maximum SBP has also been described to be a strong predictor of stroke, independent of mean SBP. In patients with treated

hypertension, higher residual variability in SBP is associated with a high risk of vascular events (50). Thus, understanding the pattern of BP in daily life has implications, and treating elevated BP is cheaper than doing nothing. Combining antihypertensive agents has been shown to be more efficacious at lowering SBP than uptitration of monotherapy (51).
Good treatment adherence to antihypertensive drugs has been shown to lower CVD events by 19% (52), but adherence remains a major challenge. It is important to explain to an individual why it is necessary to take for instance three medications for a syndrome without symptoms.

The results of the SPRINT trial have been subject of debate, mostly because BP was measured during an unattended session, which is known to give a lower value than measurement in day-to-day clinical practice. BP of 140/90 mmHg measured as regular office BP has been described to correspond to 125/82 mmHg if an unattended automated office BP is measured after the subject has been left alone in the room for 5 minutes (53). Moreover, the medication regime in the SPRINT trial was adapted to reach the respective targets, including for instance discontinuation or decreasing the dose of diuretics. This occurred more often in those assigned to the target of <140 mmHg. In high-risk patients, this may have yielded worse outcomes. Indeed, an opinion article noted that based on the SPRINT results, it can be estimated that out of 1000 patients treated for 3.2 years, treating to <120 mmHg as compared with <140 mmHg, on average 16 persons would benefit, while 22 would be seriously harmed. 962 would not experience benefit or harm (54).

What the optimal BP target is, is a returning question as well as whether a J-curve phenomenon exists. The CLARIFY study is a prospective longitudinal registry study of outpatients with stable CAD in 45 countries, who are treated for hypertension. Results of the CLARIFY study indeed suggest a J-curve, with increased risk of the primary outcome of CV death, MI or stroke with SBP >140 mmHb, but also when SBP <120 mmHg (55).

The optimal BP target may actually depend on underlying disease and/or the coexistence of other CV risk factors. Treating hypertension encompasses more than treating BP, as multiple risk factors may together be regarded as the hypertensive metabolic phenotype. An additive effect of treatment can be obtained if for instance also dyslipidaemias are targeted, and impaired glucose tolerance or insulin resistance. The additive effect of cholesterol and BP on CHD risk had already been reported in 1992 (56). And the ASCOT-LLA demonstrated a 36% reduction in non-fatal MI and fatal CHD when hypertensive patients who were normally not deemed dyslipidaemic, received atorvastatin 10 mg, as compared with placebo, in addition to their antihypertensive therapy (16).

Thus, currently the best approach to modern treatment of BP to reduce CV risk may include RAS blockade by an ARB to reduce structural damage, reduce inflammation and possibly the risk of developing diabetes, a calcium channel blocker that compliments the ARB by potent BP reduction and by optimally reducing BP variability. In addition, a statin is indicated in most hypertensives to reduce cardiac and stroke risk, irrespective of baseline cholesterol.

Evidence suggests that a high-normal BP (130-139/85-89 mmHg) was associated with an increased risk of CV events, with an incidence of 8% in men aged 35-64 and 25% in men between the ages of 65 and 90 years (57). The ALSPAC study showed that in children of 9-11 years old, higher BMI was associated with elevated SBP (58). Another study described that childhood hypertension was associated with increased risk of premature death (57% increase when comparing first with fourth quartile)(59). In addition, midlife BP has been shown to predict future diastolic dysfunction independently of BP later in life (60). Elevated midlife, but not late-life SBP, was found to be associated with more cognitive decline during a 20-year follow-up of the ARIC study (61). These data show that investing early in those risk factors can be a valuable approach for prevention. This approach is not only dependent on medication: limiting salt intake can play an important role in reducing CHD events (62).

Glucose-lowering to reduce CV risk

T2DM is associated with a higher risk of a broad range of CV complications (63) and lower life expectancy, especially once a diabetic patient has experienced a CVD event (64). The younger one gets a T2DM diagnosis, the larger is the effect on mortality (65). In an attempt to understand what is driving this CV risk, it is interesting to compare the relationships between CHD risk and fasting blood glucose, total/non-HDL cholesterol and SBP. The curve of the relationship between fasting blood glucose and event risk is relatively flat as compared with those of cholesterol and SBP and risk (66). Thus, the biggest successes are to be made by modifying cholesterol and SBP. Indeed, lowering cholesterol with statins have been shown to lower CVD risk (67), albeit not to non-diabetes levels (68). However, it should be noted that intensive LDL-lowering does not prevent atherosclerotic disease progression in those with diabetes (69).

The Multiple Risk Factor Intervention Trial (MRFIT) showed that CV risk in diabetic patients increases with the number of risk factors, and is roughly two to three times higher compared with CV risk in nondiabetics (70). Multifactorial risk factor reduction is therefore key to lowering CV risk. A multifactorial intervention in T2DM was demonstrated to yield a progressively larger CV benefit with time, as compared with conventional therapy (71).

A meta-analysis compared the benefit of different interventions per 200 diabetes patients treated for five years. The data revealed that per 4 mmHg lower SBP, 12.5 fewer CV events were seen, and 8.2 fewer events were

seen per 1 mmol/L lowering of LDL-c. The benefit of lowering blood sugar with traditional glucose lowering therapies was smallest, namely 2.9 fewer CV events per 200 patients treated for five years, per 0.9% lower HbA1c (72).

In the factorial ADVANCE trial, T2DM patients treated with the combination of perindopril and indapamide showed a lower mortality risk, but intensive glucose control towards HbA1c <6.5% did not yield a benefit (73). Data of a 6-year post-trial follow-up showed that those who had previously been assigned to active BP-lowering treated still had reduced mortality risk; the effect was attenuated as compared with the effect at the end of the trial, but the mortality benefit was still significant (73).

Efficacy and safety of novel glucose-lowering therapies

After the ACCORD study reported a higher rate of death from any cause in the group receiving intensive glucose lowering treatment as compared to those assigned to receive standard therapy (74), the FDA and EMA issued that new diabetes drugs should demonstrate CV safety with meta-analysis and CV outcome trials. Before ACCORD, other studies of glucose-lowering drugs had also demonstrated increased CV risk.

The TECOS CV outcome study demonstrated safety of the dipeptidyl peptidase 4 (DPP4) inhibitor sitagliptin in comparison with placebo added to usual care, with a neutral effect on the primary endpoint, the secondary endpoint, hospitalisation for HF and death from any cause (75). The LEADER trial then showed a 15% lower event rate of the primary outcome and a 13% reduction in death from any cause with the GLP-1 receptor agonist liraglutide, over a period of 54 months (76). This suggests that treatment with this GLP-1 analogue has an early effect on the atherosclerotic process.

Another new class of glucose-lowering drugs is formed by SGLT2 inhibitors, which diminish renal glucose reabsorption in the proximal tube. Empagliflozin is the first drug in this class that has been tested according to the FDA mandate. The EMPA-REG OUTCOME study demonstrated a reduction of CV mortality by 38% in T2DM patients treated with empagliflozin, as compared with those on placebo, in addition to standard care. The primary outcome was significantly reduced 14%, which implied superiority. Death from any cause was reduced by 35% and hospitalisation for HF was reduced by 32%. The differences between the treatment arms seemed to appear already within six months (77). This was different from observations in the LEADER trial, suggesting a different underlying mechanism. Empagliflozin has also been described to slow progression of kidney disease in those with T2DM (78).

Thus, in addition to BP and cholesterol lowering, CVD and renal benefit can be achieved in T2DM patients with new diabetes drugs. The new antidiabetic drugs target various CVD mechanisms, and are safer than conventional agents because they cause less hypoglycaemia. Some also induce weight loss. The new agents may be part of lifetime CV risk management, which will be most effective if all CV risk factors are targeted already at the 'prediabetic' stage.

Managing patients with comorbidities

Although many patients have multiple diseases and risk factors, evidence is lacking on how best to manage patients with comorbidities. Also the effect of comorbid conditions on risk stratification is often unclear. The burden of comorbidities is growing as a consequence of an aging population, and better medical care leading to better survival in many conditions. The number of chronic disorders increases with age. About a quarter of people of at least 70 years old have four or more disorders, and up to about 10% of people aged over 85 have at least 7 disorders (79).

Most RCTs select patients younger than 75 years old, and comorbidities are often excluded, especially cancer. Consequently, the patient population in RCTs reflects less than 50% of the population. Men are often overrepresented in RCTs, so also female-specific risk factors for CVD may need to be considered, such as preeclampsia, which increases CVD risk by a factor 1.5-2.5 (80).

Comorbidities often increase the risk profile of a patient, which in turn may affect treatment targets, for instance lower LDL-c goals in those with higher CV risk (7). It also means that the therapeutic approach should have multiple goals, possibly targeting BP, lipids, HbA1c and BMI if needed. Lifestyle interventions are crucial in this approach.

Comorbidities may not only affect risk assessment, but also the diagnostic process. For instance, data suggest that an exercise ECG-test to check for coronary artery disease is less informative in diabetic patients, as more CV events were seen after a negative stress test in diabetics than non-diabetics (81). Moreover, it has lower prognostic value for these patients (82).

Managing patients with chronic kidney disease

Patients with renal failure deserve specific attention. Renal disease is quite prevalent, with a median prevalence worldwide of 7.2% in persons aged at least 30 years. In those over 64 years old, prevalence is estimated to vary between 23.4 and 35.8%. The most common cause of chronic kidney disease (CKD) is diabetes (83).

Five different stages of CKD are recognised by the National Kidney Foundation, based on the eGFR. The most severe stage is end stage renal disease (ESRD), when eGFR <15 ml/min/1.73m2, which necessitates dialysis. While some physicians may be afraid for their patients to progress to the next stage of CKD, an analysis of 5 years of follow-up of the Kaiser Permanente database shows that the risk of death is far greater than the risk of need for renal replacement therapy. Death in these patients is often driven by CV reasons (84). Indeed, persons with low eGFR have been described to have high risk of CVD (85). Therefore, efforts to reduce mortality in a population with renal failure should be focussed on treatment and prevention of CAD, congestive

HF, DM and anaemia.

Patients with CKD do not necessarily have worse lipid profiles; while the majority of those with nephrotic CKD stage 1-4 have high LDL-c (>130 mg/dL), this is the case for only 10% of those with non-nephrotic CKD. Thus, in the majority of people with renal dysfunction, there is no such thing as a CKD-associated dyslipidaemia. The 4D study (86) and the AURORA study (87) tested the efficacy of rosuvastatin 10 mg/day in patients with ESRD. These studies showed no change in CV mortality between the active treatment and placebo arm, over a follow-up of 4 and 3.8 years, respectively. In the AURORA trial, the lack of a clinical effect was not due to a lack of response to statins; both LDL-c and C-reactive protein levels were reduced in those treated with rosuvastatin (87). Surprisingly, the results of the 4D trial did not affect prescription behaviour: the haemodialysis population continued to receive statins (88). In a post-hoc analysis of the 4D trial, however, a clinical benefit was seen with atorvastatin treatment in patients with both diabetes and ESRD (89).

The CARDS study evaluated the effect of statins in diabetic patients, and compared the effect in patients with eGFR above vs. below 60 ml/min/1.73m2. Statin treatment gave a CVD benefit, irrespective of renal function (90). Thus, unlike in ESRD, in patients with a minor renal dysfunction, initiating a statin at a low dose is beneficial. The CARDS study results also suggested that statin atorvastatin therapy had a positive effect on preservation of eGFR (90). Studies have also shown that increasing the dose of statins provides a dose-dependent reduction of CV risk, and does not come with a higher risk of AEs (90, 91). The preservation of eGFR by statin treatment also seemed to be dose-dependent (92). It should be note that different statins and doses are not equal with regard to AEs and CKD outcomes in those with renal disease, as was revealed in the PLANET study (93). More specifically, while high-dose rosuvastatin lowered lipid concentrations to a greater extent than high-dose atorvastatin, atorvastatin 80 mg lowered the urine protein:creatinine ratio (UPCR) more than did rosuvastatin 40 mg in patients with diabetes who had proteinuria. Thus, atorvastatin seemed to have more renoprotective effects in this studied chronic kidney disease population (93). Also in patients with renal disease, treatment with atorvastatin needs down-titration, since this statin has the lowest renal excretion rate (<5.%).

What do the guidelines say?

International guidelines

In 2016, a joint task force of the European Society of Cardiology (ESC) and other societies on CVD prevention published new European Guidelines on CVD prevention in clinical practice (94). These guidelines recommend systematic CV risk assessment in individuals at increased risk (class I C recommendation), i.e. with a family history of premature CVD, familial hyperlipidaemia, major CV risk factors, or with comorbidities that increase CV risk. Also, systematic CV risk assessment may be considered in men >40 years of age, and in women of >50 years old or post-menopausal with no known CV risk factors (class IIb C).

Different risk assessment scores exist, for instance the Framingham risk score, the SCORE system and QRISK 1 and 2. It should be noted that these guidelines are based on different populations and age groups. Some groups in the population may not be represented in a given risk assessment score. The new European Guidelines (7) recommend using the SCORE system to estimate CV risk in adults >40 years of age, unless they are automatically categorised as at high-risk or very high-risk, based on documented CVD, diabetes mellitus (>40 years), kidney disease or a highly elevated single risk factor (7). Different versions of the SCORE system have been made that take into account the overall risk profile of a country. For SCORE, Russia is considered a very high-risk country.

The risk category an individual falls into along with measurable risk factor levels, affect the decision whether or not to give drug therapy, in addition to lifestyle advice to reduce CV risk. A recent study compared the indications of the European and American guidelines for statin therapy and quantified whether adding a coronary artery calcium (CAC) score to the risk stratification strategy could help select patients who need or do not benefit from statin therapy. This prospective study, with a mean follow-up duration of 10.4 years, found that taking CAC score into account can help identify individuals at intermediate risk who can avoid statins (95).

In fact, Guidelines stress the importance of improving lifestyle and reducing burden of major CVD risk factors, especially in younger adults. Smoking should be avoided in all forms, diets should be low in saturated fat, and wholegrain products, vegetables, fruit and fish should prevail. The European Guidelines set a minimum of 150 minutes of moderate aerobic physical activity per week, or 75 minutes of vigorous aerobic exercise, or a combination thereof. BMI is ideally between 20 and 25 kg/m2, and waist circumference should not exceed 94 cm in men or 80 cm in women (7).

Advising patients on lifestyle improvement pays off and deserves more attention. In particular, smoking can reduce CV risk by about half, as a secondary prevention measure. Even if a person quits smoking at age 60, still some years alive can be gained, as well as quality of life.

The European Guidelines recommend a BP of <140/90 mmHg. Concerning lipids, three risk categories are distinguished, each with their own LDL-target. Very high-risk patients should work to achieve an LDL-c level below 1.8 mmol/L (<70 mg/dL0, or a reduction of at least 50% if baseline is between 1.8 and 3.5 mmol/L (70-135 mg/dL). For high-risk

patients, the target is set at <2.6 mmol/L (<100 mg/dL), or at 50% if baseline is between 2.6 and 5.1 mmol/L (100-200 mg/dL). Individuals at low to moderate risk should aim to have their LDL-c drop below 3.0 mmol/L (<115 mg/dL) (7).

The Guidelines do not give a target level for HDL-c but state that >1.0 mmol/L (>40 mg/dL) in men and >1.2 mmol/L (>45 mg/dL) in women indicates low risk. Specifically, pharmacological intervention to increase HDL-C level is not recommended (level of evidence IIIA), since, so far, there are no evidence-based data to support this intervention. Higher TG levels indicate a need to look for other risk factors and exclude secondary causes of hypertriglyceridaemia. In some patients with very high TG levels (> 10.0 mmol/L) a combination therapy (statins+ fibrates+omega 3 FA) is indicated to reduce the risk of acute pancreatitis. HbA1c goal is set at <7% (<53 mmol/mol) (7).

The ESC/EAS guideline on Dyslipidaemia (10) regard CKD as a CAD risk equivalent, for which LDL-c lowering is the primary target of therapy. In CKD stages 2-4, a LDL-c target of <70 mg/dL (1.8 mmol/L) is recommended. Statin therapy has been shown to be safe and efficacious to lower CVD risk in those with renal dysfunction, while no benefit of LDL-lowering treatment has been found for those with ESRD (86, 87).

Special patient groups

Considering that SCORE is based on a large dataset of European men and women aged 40-65 years old, how should one assess and communicate CV risk in young people? The first option might be to use a relative risk chart, as shown in the European 2016 guidelines (7), which takes into account cholesterol and BP levels and smoking status. Relative risks are, however, hard to communicate; the urgency is hard to grasp for most individuals. A better way may be to speak of 'risk age', by comparing an individual's risk level to that of an older individual without risk factors. Speaking of 'heart age', and considering lifetime CVD risk, with the help of the aforementioned JBS3 risk calculator may speak to the patient even more. This calculator shows the age of the heart based on the risk profile, as compared to calendar age. Also, it demonstrates how heart age will be lowered to closer to the calendar age, if risk factors are eliminated.

In those over 60 years, age is the main driver of risk, so LDL-c and BP-lowering is recommended in all by the European guidelines, based on SCORE in higher ages. However, the written explanation is a bit different from the SCORE table, in that no specific lipid recommendations are given for the elderly, except that caution is required in the very elderly (>80 years), as evidence on primary prevention is limited. In older patients, thresholds may be interpreted more leniently, as it is important to consider the patient's situation and preferences.

If BP >160 mmHg in patients older than 60 years, SBP should be brought to between 140 and 150 mmHg. JNC8 (2014) recommends initiating antihypertensive treatment in all those over 60 years with ≥150/90 mmHg.

Something to look out for in young individuals is familial hypercholesterolaemia (FH). The European guidelines acknowledge a family history of premature CVD to be a risk modifier with reclassification potential (7). If someone with LDL-c >4.9 mmol/L speaks of premature CVD in a first-degree relative, the likelihood of this reflecting a monogenic disorder is relatively high. FH is an autosomal dominant disorder that increases the risk of having CHD in the heterozygous (HeFH) form, and even stronger in the homozygous (HoFH) form. FH is greatly underdiagnosed and as a consequence, undertreated (96).

HeFH and HoFH individuals have likely been exposed to elevated LDL-c levels from birth onwards, and indeed the disease is characterised by visible and invisible cholesterol accumulation. It pays off to treat FH individuals early, so if an FH patient is identified, the family may be involved in the diagnostic process. Diagnostic criteria are fairly straightforward; the Dutch Lipid Network Criteria (DLNC) are commonly used to reach a probable or definite FH diagnosis (96). The 2013 EAS Consensus Statement on underdiagnosis and undertreatment of FH also includes a list of clinical situations that point at the need for opportunistic, universal and cascade screening for FH (96).

Russian National guidelines

Many Russian national research societies are involved in composing national CVD guidelines. Russian guidelines are often tailored from the ESC and other international guidelines, and, as a rule, include data from national registers and original epidemiological research. In addition to composing Russian guidelines, several international guidelines and relevant consensus documents have been translated into Russian (see: www.lipidology.ru).

The fifth update of the Russian national lipid guidelines have been published in 2012. They recommend targeting LDL-c in very high-risk and FH patients, using different LDL-targets for different risk categories, similar to the European Guidelines 2011 (<3.5 mmol/L in low-risk, <3.0 mmol/L in moderate risk, <2.5 mmol/L in high-risk, and <1.8 mmol/L in very high-risk patients). For FH patients, the EAS/EAS Guidelines along with International FH Foundation Guidelines (97) recommend <2.5 mmol/L for those without CHD, and <1.8 mmol/L for those with CHD (the International FH Foundation Guidelines are translated into Russian for better penetration into routine clinical practice).

A Russian expert consensus statement on statin therapy (98) followed EAS in recommending prioritising patients with high and very high CV risk, and it advocates targeting LDL-C <1.8 mmol/L or a reduction from baseline of 50%. Maximum statin exposure on the long term is recommended, with atorvastatin 40-80 mg/day or equivalent. Of note, the Russian Ministry of Health ordered on July 2015 to use high-dose statins (atorvastatin 80 mg, rosuvastatin

40 mg or simvastatin 40 mg/day) in patients with non-STEMI ACS.

Criteria for metabolic syndrome in Russia consist of central obesity (waist >80 cm in females and >94 cm in men) as the main criteria and two of a list of additional pathophysiological levels of risk factors, including BP, lipids and sugar metabolism. Instead of using LDL-c, ApoB is informative, as it is more related to the level of unfavourable cholesterol particles.

The Standards of Care document (99) is a useful evidence-based guidelines document on diabetes care, composed by the Russian Association of Endocrinologists. It suggests targets for HbA1c, depending on age and presence of macrovascular complications and risk of hypoglycaemia. Also lipid targets in T2DM patients are given, as well as SBP and DBP goals.

The hypertension guidelines are also based on the European ones (2013) and SBP <140 mmHg is recommended for all. In T2DM, DBP <80 mmHg is advised. In patients with arterial hypertension at moderate or high risk, statins are also recommended to target an LDL-c level of <3.0 mmol/L. In patients with hypertension and dyslipidaemia, several tests are recommended (in line with ESC/ESH) to assess clinical status and risk. Non-invasive tests can also serve to stimulate compliance.

A guideline on cardio-nephroprotection strategies has been published in 2014 (100), which formulates diagnostic criteria for CVD and recommends doses of drugs for different stages of renal failure.

As far as paediatric guidelines are concerned, the American (NIH) (101) and European (EAS)(102) guidelines can be followed, the latter of which has been translated into Russian. In children, it is important to be aware of the possibility of severe monogenic lipid disorders, as they are often associated with a high risk of disease.

Russian epidemiology data on risk factor management

National data should be appreciated when considering the guidelines; for instance, the observation that 33.5% of Russian men and 46.3% of women aged 40-69 years have total cholesterol of over 6.2 mmol/L (101). It is therefore essential to know the current situation, by monitoring major CVD risk factors. In addition, it is important to monitor the quality of treatment, as has been done in DYSIS I&II (103). Mortality from CVD has steadily risen in Russia since 1960 (2697/100 000 persons) to a peak in 2003 of 923.7 per 100 000 persons. Since 2003, a decline has been observed, to 635.3 per 100 000 in 2015.

Blood pressure

In Russian men, elevated SBP is the strongest risk factor contributing to CV mortality (47%), while in women this takes the second place with 55%, and diastolic BP (DBP) leads the list with 65.9% attributable risk. According to FSI "National Research Center for Preventive Medicine" data (104), the prevalence of hypertension is on the increase. In 1993 hypertension was observed in 33.7% of the male population and by 2013, it was already observed in 41.9% of males. High intake of salt plays a major role in the development of hypertension. The prevalence in 2013 increased in men to 47,2% and decreased in women to 39,6%, respectively (105). While 42% of men and 61% of women receive treatment for hypertension, a recent publication described that only 42% of men and 53.9% of women receive effective treatment. Only 16% of men and 31.1% of women have their BP controlled (105). Indeed, individuals with ineffectively treated hypertension showed the poorly-controlled risk factor profile, not limited to BP, but also concerning waist circumference, BMI, glucose levels, heart rate, total cholesterol, HDL-c, TG and LDL-c levels. Between 2012 and 2014, ACE inhibitors were the most prescribed antihypertensive drugs, followed by beta-blockers. It is striking that over half of patients only take one BP-lowering medication (men: 57.9%, women: 55.3% on monotherapy). 32.3% and 33.3% respectively get prescribed two drugs, and only 4.2% and 11.4% receive three or more antihypertensive agents (105)

In those at moderate risk, 51.7% of men on monotherapy, 68% of those taking two agents and 55.9 of men receiving three drugs, reach their BP target. More women at moderate risk achieve BP goal: 71.9%, 73.4% and 78.8% for those on 1, 2 or 3 drugs respectively. In high-risk men, only 18.7%, 23.8% and 28.7% reach target BP in the respective drug regimens, and for high-risk women the percentages are 24.8%, 23.7% and 27.9% (104, 105).

Lipids

Dyslipidaemia is prevalent in Russia, with 62% of people having total cholesterol >5.2 mmol/L and 44% >6.2 mmol/L (107). Another source reported that at least half of Russian adults have hypercholesterolaemia (total cholesterol >5.0 mmol/L, men: 58.4%, women: 57.9%) or LDL>3 mmol/L (men: 62,2%, women: 57.3%). 16.4% of men and 21.3% have aberrant HDL-levels (1.0/1.2 mmol/l, respectively) and 30.2% of men and 20.1% of women show triglyceride abnormalities (>= 1,7 mmol/l)(106).

Awareness about lipid disturbances is low, with 17.8% of men and 30.9% of women without CHD are aware of their cholesterol levels. Awareness increases with age in both sexes; from 10.1 in those aged 25-34 years, to 24.3% in those 55-64 years old. 19.1% of women aged 25-34 were aware of their lipid profile, but this increased to 43.6% in those 55.64%. In people with CHD, awareness is better; irrespective of age (35.9% in men, ranging from 22.6% (25-34 years) to 45.3% (55-64 years) I men and 35.7% in women (16.6% to 55.8% in those age categories).

When looking at the proportion of individuals receiving statins in different SCORE risk categories, it can

be concluded that almost no statins are given as primary prevention, in individuals without CAD or a serious event, as 0.2% of men and 0.3% of women with SCORE 1 receive statins. With SCORE 1-4 this is 0.7% and 2.9% respectively, and with SCORE 5-9, 1.2% of men and 4.4% of women receive statins. In those with SCORE 10+, 0.5% and 2.3% are on statins (105). In high risk population 9.9% of men and 7.9% of women take statins; the proportion of men and women who reach the LDL-c target of ≤1.8 mmol/l are 13.0% and 3.6% respectively (104, 105).

Smoking

A positive trend can be appreciated concerning smoking prevalence. Smoking has dropped from 60.3% in men in 1993 (108) to 39.1% in 2013 (109), and 41.4% according to Rosstat in 2011 (110). Russian women smoke less, but prevalence has increased from 9.4% to 13.6% over this period (9.7% according to Rosstat in 2011). In a Moscow representative sample, 62.3% of men and 25.8% of women smoked. In a subpopulation of doctors, percentages were 51.3% and 27.3%, and in teachers it was 43.3% and 11.2% for men and women respectively. The epidemiological study (ESSE-RF (109)) has shown that the prevalence of smoking varies considerably per region (between 18.7 and 34.6% of participants). Young people smoked most, with 47.8% of men between 25-34 and 19.9% of women in this age group, as compared with 35.5% of men and 5.9% of women aged 55-64 years old. Lower educated people smoke more than those with higher education, in men and women.

Obesity

Among the various risk factors in the Russian Federation over the past 20 years, obesity changed most. In general, a two-fold increase in the prevalence of obesity among men was observed over the past 20 years. In 1993, obesity was observed in 10.8% of the male population (111), and in 2013 (107), it was observed in 26.6% of males (and 30.8% in women). Recent data showed that the prevalence of obesity (BMI≥30.0 kg/m2) was 29.7% in the total population (107).

Moreover, it also revealed an increase in the prevalence of obesity with age, measured by body mass index (BMI In the Russian population, 26.6% of men and 24.5% of women in the age group between 35 - 44 years, 31.7% of men 40.9% and women aged 45 - 54 years and 35.7% of men and 52.1% of women in the age group of 55 - 64 years, respectively, suffered from obesity (107). More detailed data is needed on the prevalence of obesity and clinical peculiarities in the Russian Federation.

It should be noted that a J-shaped curve is seen for the risk of CV death across BMI categories, with the lowest risk of death from CVD seen in men and women with BMI 24-26. A U-shaped curve is observed for all-cause mortality with the lowest point in the same category (112).

Obesity and hypertension are pathogenically closely related. The problem of comorbidities of hypertension and obesity (early disability, increased risk of cardiovascular complications and premature mortality when compared with the general population) is the centre of attention of the healthcare system. Obesity is not only an independent risk factor for CV complications but also a possible trigger for the development of hypertension. Obesity needs more attention for CV prevention purposes, also because its presence often co-exists with other risk factors (113, 114).

Metabolic abnormalities are common in obesity, but do not affect all obese people. About 10 - 25% patients with obesity, as well as a major proportion of patients with morbid obesity, demonstrated an absence of metabolic changes in carbohydrate and lipid metabolism. These “metabolically healthy but obese” individuals are insulin sensitive, have normal BP, a favourable lipid profile, a lower proportion of visceral fat, less liver fat despite having an excessive amount of subcutaneous fat (115).
On the other hand, a subset of normal weight individuals suffer from metabolic disturbances that are characteristic of obesity. These patients are called “metabolically obese, normal weight individuals”.
Thus, the group of obese patients is very heterogeneous. Although the theory of various phenotypes of obesity has been discussed for a long time in the scientific community, there is insufficient data on the population level prevalence and significance of each phenotype in the development of obesity-associated diseases (CVD, DMT2, NAFLD) (115).

Physical inactivity

The ESSE-RF study found that almost half (46.8%) of women and 37.6% of men aged 25-34 years does not achieve recommended doses of physical activity (150 minutes of moderate or 75 minutes of intensive physical activity per week). People in higher age categories are less inactive. With regard to education, those who received higher education are less often inactive than those who followed only lower education. Evaluated regions showed inactivity percentages varying between 27.9% and 47.8% (109).

Dietary patterns

An unhealthy diet plays a major role in the increasing prevalence of obesity. Fruit and vegetable consumption is considered adequate at at least one a day, and additionally it is recommended to eat fish at least twice a week. Especially young (25-34) men and women do not meet these recommendations, with 57.2% of men and 41.3% of women having inadequate fruit and vegetable consumption, according to the ESSAY-RF study. In the age group of 55-64, these percentages are 42.1% and 32.2% respectively. Inadequate fruit and vegetable consumption is more common

in higher vs. lower educated people (37.3% vs. 46.6%). In all categories, inadequate consumption was more prevalent in men than in women (109).

Inadequate consumption of fish was observed in 36.9% of Russians, most often in men than in women of young and middle age groups (38.8 and 34.2%, respectively). Men less often showed inadequate fish consumption (109).

According to ESSE-RF 49.9% of patients consume excessive quantities of salt, more often men than women (54.2% and 47.1%, respectively) (109).

Alcohol consumption

Contradicting numbers have been published on the sales of alcohol per capita in Russia. In data on the period between 2000 and 2015, Rosstat documents an increase from 8 L/year per capita in 2000, towards over 9.5 L in 2007, after which sales decrease to 7 L/year in 2015 (116).

According to a ranking of countries by level of alcohol consumption of the World Health Organisation (WHO) of 2010, Russia consumes 15.1 L/year per capita. WHO data of 2005 say that in Russia, 63% of alcohol consumed was strong spirits, 33% beer and 1% wine. Rosstat states that in 2011 alcohol sales consisted of spirits for 55%, of beer for 32% and of wine for 13%.

In the ESSE-RF study in 13 regions of the Russian Federation in 2012-2014, men indicated to prefer strong alcohol, and women had a preference for wine. In the survey, 21.6% of men and 24.1% of women said they drink only little alcohol, while the majority (72.5% of men and 73.8% of women) admitted to drinking moderate levels of alcohol. 5.9% of men and 2.1% of women confessed to drink excessive amounts of alcohol (109).

Although it is difficult to collect trustworthy numbers, a study in 7815 men aged 40-59 years old showed that risk of death from stroke increases with alcohol consumption, up to a relative risk of 1.8 with consumption of more than 168 g per week, as compared with those who do not drink. While 1-84 grams of alcohol was associated with RR 0.9, those consuming 84-168 grams per week showed an RR of 1.4. It was concluded that 10 grams of pure ethanol increases the risk of death from a stroke by 1% (unpublished data).

An increase in mortality from diseases of the digestive system comes about in the backdrop of decrease in morbidity due to viral hepatitis and alcoholism. Thus, according to the Federal State Statistics Service for the past 14 years, the number of reported cases of hepatitis B decreased from 62000 to 1900 cases, hepatitis C from 30800 to 2200. The incidence of alcoholism has been two-fold decreased from 2003 to 2014. Today non-alcoholic fatty liver disease (NAFLD), the most common among the gastrointestinal disorders, is closely linked to obesity and it is currently one of the major causes of liver fibrosis.

CV risk management in Russia

As advocated by current guidelines, risk factors should not be addressed in isolation, but the patient as a whole should be considered. All risk factors should be taken into account to more accurately determine an appropriate threshold to start therapy and set treatment goals. In this process, both drug and non-drug treatments should be employed.

When using the SCORE risk assessment method, it should be noted that Russia remains a high CVD risk country. In those with SCORE >5%, 40.6% of men without CVD have high risk; thus before they get a diagnosis. 5.1% of women with SCORE >5% are at high risk (117). Higher CV risk in men is associated with low education (OR: 1.71, 95%CI: 1.06-2.77, P=0.029), medium education (OR: 1.47, 95%CI: 1.19-1.81, P<0.001), heart rate >80 bpm (OR: 2.88, 95%CI: 2.23-3.70, P<0.001) and heavy drinking (OR: 2.23, 95%CI: 1.42-3.49, P<0.001). In women, high CV risk is particularly seen when heart rate >80 bpm (OR: 1.66, 95%CI: 1.33-2.06, P<0.001), abdominal obesity (OR: 1.49, 95%CI: 1.24-1.79, P<0.001) and heavy drinking (OR: 3.25, 95%CI: 1.44-8.61, P<0.001).

The DYSIS study found that the mean LDL-c concentrations in people in different risk categories were similar (2.7-2.9 mmol/L), despite the fact that different targets are recommended for those with moderate, high or very high risk. Among very-high risk patients, only 12.2% reached LDL-c target<1.8 mmol/l, and in the high and moderate risk categories target achievement was 30.3% and 53.4% respectively (103).

Data collected in the outpatient registry of cardiovascular diseases in the Ryazan region (REKVASA Registry) can serve as an interesting example of what can be achieved when emphasis in cardiology is switched from treating disease to prevention. The Registry includes data of patients with hypertension, ischaemic heart disease (IHD), congestive HF (CHF) and/or atrial fibrillation (AF). Outpatient cards of patients who visited a general practitioner or cardiologist in three outpatient clinics of Ryazan and the Ryazan Region were analysed, and 3300 of those were included in the registry. Endpoints (hospital admission, ambulance call, surgical intervention due to CVD, myocardial infarction, stroke and death) were recorded, and diagnostics and treatment quality were estimated in 600 randomised patients called to an outpatient clinical 12 months after the enrolment in the registry (118).

The ARGO-2 study assessed lipid-lowering therapy with rosuvastatin in high and very-high cardiovascular risk patients in outpatient practice. 10547 patients of 30 years and older, who visited an internist or cardiologist in a district outpatient clinic between October 2013 and July 2014, filled a questionnaire and had their TC measured. When indicated according with guidelines, physicians prescribed rosuvastatin therapy, and TC was measured again after one month. The

prescribed dose of statin was to be determined by the physician. The majority (62.5%) of patients received 10 mg per day, 27.3% got 20 mg per day, and other doses ranging from 2.5 to 40 mg per day, were all given in less than 10% of patients. The average dose of rosuvastatin prescribed increased with higher baseline TC level, in particular with baseline TC >6 mmol/L. A dose-dependent TC-lowering effect was observed. The ARGO-2 study showed that in real clinical practice, maximum doses are rarely prescribed in patients with high or very-high risk, despite their proven lipid-lowering effect (119).

In men over 45 years old, over half the population are at high CV risk. CV risk in women is lower than in men when they are under 45, but their risk profiles resemble that of men from 45 years of age onwards (120). These data show that currently people are not treated effectively enough according to International and national Guidelines. This should be seen as an urgent call for action: a lot more could be done at the level of prevention. A challenge is implementation into primary care. In 2015-2016 this has been attempted by the free distribution of >16500 copies of a pocket guidelines on 'dyslipidaemia and atherosclerosis' across Russia.

Final thoughts

The epidemiological data suggest that there is ample room for improvement in the prevention and management of CVD in Russia. Levels of several risk factors are improving, thus preventive efforts pay off. More prevention is needed, however, to lower the CVD burden. Based on the available evidence, a broad and early approach is recommended. Considering the geographic variation of risk factor prevalence observed in Russia, establishment of regional prevention programs covered by government and Ministry of Health is worth looking into.

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