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ISSUE-3 CARDIOLOGY

## Prime Time News



## Indian Scenario



Congenital heart disease (CHD) has not been studied thoroughly in India as in western countries. There are only few studies of the prevalence and pattern of CHD in India. The present study reports prevalence and pattern of CHD at a tertiary care hospital in Uttarakhand, India.

## Images that Teach



## Views and Reviews



Hypertension and chronic kidney disease (CKD) are inextricably linked. The causal nature of the relationship is bidirectional. Patients with CKD are more likely to have high-risk hypertension phenotypes, such as masked and sustained hypertension, and are at increased risk for cardiovascular disease.



Congestive heart failure (CHF) is a major cause of morbidity, mortality, and health care expenditure. Although the role of renal artery stenosis (RAS) in CHF has been known, there are a number of areas of uncertainty.

## Top Stories



## Practice Guide



Despite the differences in statin intensities, safety concerns, use of risk estimators, or treatment of specific patient subgroups, there are more similarities than differences between the guidelines from both a clinical and practical point of view. Physicians ought to understand both similarities and differences in guideline recommendations to make the right decision regarding statin therapy for individual patients.

## Practical Case Study in Hypertension



A 70-year-old, Caucasian male, diagnosed of hypertension at 55 years of age, was referred by his family physician to perform a 24-h ambulatory blood pressure monitoring (ABPM) and to evaluate uncontrolled hypertension. He was treated with four antihypertensive drugs. A 24-h ABPM was performed, and the final diagnosis was uncontrolled diurnal hypertension.

## Clinical Update



Chronic heart and lung diseases are very common in the elderly population. The combination of chronic heart failure and chronic obstructive pulmonary disease (COPD) is also common and, according to current guidelines, these patients should be treated for both diseases.

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# Alterations in the Gut Microbiome and Metabolism with Coronary Artery Disease Severity

Coronary artery disease (CAD) is associated with gut microbiota alterations in different populations. Gut microbe-derived metabolites have been proposed as markers of major adverse cardiac events. However, the relationship between the gut microbiome and the different stages of CAD pathophysiology remains to be established by a systematic study.

Based on multi-omic analyses (sequencing of the V3-V4 regions of the 16S rRNA gene and metabolomics) of 161 CAD patients and 40 healthy controls, we found that the composition of both the gut microbiota and metabolites changed significantly with CAD severity. We identified 29 metabolite modules that were separately classified as being positively or negatively correlated with CAD phenotypes, and the bacterial co-abundance group (CAG) with characteristic changes at different stages of CAD was represented by *Roseburia*, *Klebsiella*, *Clostridium IV* and *Ruminococcaceae*. The result revealed that certain bacteria might affect atherosclerosis by modulating the metabolic pathways of the host, such as taurine, sphingolipid and ceramide, and benzene metabolism. Moreover, a disease classifier based on differential levels of microbes and metabolites was constructed to discriminate cases from controls and was even able to distinguish stable coronary artery disease from acute coronary syndrome accurately.

Overall, the composition and functions of the gut microbial community differed from healthy controls to diverse coronary artery disease subtypes. Our

study identified the relationships between the features of the gut microbiota and circulating metabolites, providing a new direction for future studies aiming to understand the host–gut microbiota interplay in atherosclerotic pathogenesis.

*Source: Liu, H., Chen, X., Hu, X. et al. Microbiome (2019) 7: 68. https://doi.org/10.1186/s40168-019-0683-9. © The Author(s). 2019.*

# Red Cell Distribution Width and Preeclampsia: A Systematic Review and Meta-analysis

Preeclampsia is a serious pregnancy-related disease which may lead to adverse health effects to the mother and fetus. Besides many publications on the association of red cell distribution width (RDW) and preeclampsia, there has been no published meta-analysis. This necessitated the present systemic review and meta-analysis to assess the RDW in relation to preeclampsia.

Preferred Reporting Items for Systematic Reviews and Meta-Analyses guideline was followed. Relevant published studies were searched in PubMed, Cochrane library, Google scholar, Scopus, Embase and CINAHL (using the term "Preeclampsia OR eclampsia AND red cell distribution width OR red blood cells). Modified Newcastle – Ottawa quality assessment scale was used for critical appraisal of retrieved studies. Pooled meta logistic regression was computed using OpenMeta Analyst software. Subgroup and meta-regression methods were performed to analyse the heterogeneity.

Eleven case control studies were included in the meta-analyses with a total of 951 cases (preeclampsia) and 2024 controls. The mean (SD) of the RDW level was significantly higher in women with preeclampsia compared to controls [15.10 (2.48) % vs. 14.26(1.71) %, $P < 0.001$]. The mean difference was 0.85, 95% CI = 0.26–1.43. Due to a high heterogeneity ($I^2 = 90.45$, $P < 0.001$), the continuous random effect model was used.

Eight studies compared RDW level in the mild ($N = 360$) with severe cases ($N = 354$) of preeclampsia. The RDW level was significantly higher in women with severe preeclampsia compared to those with mild preeclampsia [15.37 (2.48) % vs. 14.037(1.79) %, $P < 0.001$]. The mean difference was 1.07, 95% CI = 0.45–1.70. Since there is a high heterogeneity [$I^2 = 76.67$, $P < 0.001$], the continuous random effect model was used.

Through the meta-regression model, except for the region of the study ($P < 0.001$), none of investigated variables (age, parity, quality of the study) was significantly associated with the investigated heterogeneity. The outliers (3 studies) were removed to reduce the heterogeneity. The pooled meta-analysis of the remaining 8 studies showed a significant difference in the RDW between preeclamptic women compared with the controls. The mean difference was 0.93, 95% CI = 0.56–1.31, $P < 0.001$. Because of heterogeneity [$I^2 = 69.6$, $P = 0.002$], the continuous random effect model was used.

Red cell distribution width level was significantly higher in women with preeclampsia compared to controls. Similarly, women with severe preeclampsia had significantly higher RDW than those with the mild form.

*Source: Adam, I., Mutabingwa, T.K. & Malik, E.M. Clin Hypertens (2019) 25: 15. https://doi.org/10.1186/s40885-019-0119-7. © The Author(s). 2019.*

# Prevalence and Pattern of Congenital Heart Disease in Uttarakhand, India

**Nowneet Kumar Bhat, Minakshi Dhar, Ritesh Kumar, Anubhav Patel, Anil Rawat, Braham Prakash Kalra**

Congenital heart disease (CHD) has not been studied thoroughly in India as in western countries. There are only few studies of the prevalence and pattern of CHD in India. The present study reports prevalence and pattern of CHD at a tertiary care hospital in Uttarakhand, India.

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Congenital heart disease (CHD) is one of the most common congenital defects and along with neural tube defects accounts for two-thirds of all congenital malformations [1]. Early recognition of such diseases has great implications. Despite improved medical care, CHD is considered one of the leading causes of neonatal mortality [2]. According to a status report on CHD in India, 10% of the present infant mortality may be accounted for by CHD [3]. CHD may present at different ages from birth to adolescence [2]. Many cases are asymptomatic and discovered incidentally during routine checkups [4]. Other presentations can range from cyanosis, clubbing of fingers to full blown congestive heart failure [2, 4].

Congenital heart disease has not been studied thoroughly in India as in western countries. There are only few studies of the prevalence and pattern of CHD in India. The present study reports prevalence and pattern of CHD at a tertiary care hospital in Uttarakhand, India.

Accurate assessment of prevalence of CHD in a population is critical in understanding the social and economic burdens placed on the patients and their families, demands placed on the health care system and health planning.

## Materials and Methods

The study was conducted at the Department of Pediatrics, Himalayan Institute of Medical Sciences, a tertiary

care teaching hospital at Dehradun, India. The hospital caters to patients belonging to all strata of society from Uttarakhand, western Uttar Pradesh and adjoining areas of Himachal Pradesh and Haryana. All live births at the hospital and children up to 18 y of age who presented to OPD (out patient department) and IPD (in patient department) over a period of 3 y from July 2008 through June 2011 were included in the study. A thorough history and clinical examination was carried out, and CHD was suspected in presence of a cardiac murmur, presence of cyanosis, feeding difficulty, cyanosis associated with feeding difficulty, clubbing, features of congestive heart failure and failure to thrive [5]. Those with history, symptoms or signs of heart disease were further evaluated with ECG, chest radiography and confirmation of the diagnosis was done by color Doppler echocardiographic examination. CHD was defined as the structural abnormality of heart or intrathoracic great vessels, present since birth that is actually or potentially of functional significance regardless of the age at detection, as defined by Mitchell *et al.* [5]. Only children with first time diagnosis were included and those presenting on follow up visits were excluded. Neonates less than 2 wk of age with a diagnosis of PDA were also excluded. The data was entered into a Microsoft Office Excel Spreadsheet and analysed.

## Results

During the study period 36541 children less than 18 y of age presented to the institution. Congenital heart defects were identified in 312 children (182 boys and 130 girls), thus giving a prevalence of 8.54 per 1000 children attending hospital. The boy to girl ratio was 1.4. Acyanotic heart disease was present in 234 (75%) children; 78 (25%) had cyanotic heart disease. Maximum number of cases were seen in 0–1 y age group ($n = 133$, 42.63%). The pattern of various CHDs observed is depicted in Table 1.

Ventricular septal defect followed by atrial septal defect, patent ductus arteriosus, and pulmonary valve stenosis were the commonest acyanotic congenital heart lesions, comprising 30.45%, 17.63%, 9.62% and 6.41% respectively. Tetralogy of Fallot (5.45%) followed by transposition of the great arteries (5.13%), pulmonary atresia (3.21%) and tricuspid atresia (1.92%) were the commonest cyanotic congenital heart lesions as shown in Table 1.

Of the 312 children diagnosed with CHD, 29(9.29%) underwent definitive (surgical/interventional cardiac) treatment at the authors' institution during study period.

**Table 1: Pattern of congenital heart disease in 312 children.**

| Age group → | <1 mo | | 1 mo–1 y | | 1–6 y | | 6–12 y | | 12–18 y | | Total | (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ↓ CHD | M | F | M | F | M | F | M | F | M | F | | |
| Ventricular septal defect | 10 | 9 | 12 | 9 | 14 | 16 | 9 | 3 | 10 | 3 | 95 | 30.45 |
| Atrial septal defect | 6 | 4 | 6 | 6 | 8 | 7 | 6 | 4 | 4 | 4 | 55 | 17.63 |
| Patent ductus arteriosus | 6 | 2 | 7 | 3 | 3 | 3 | 0 | 3 | 2 | 1 | 30 | 9.62 |
| Pulmonary stenosis | 1 | 2 | 2 | 3 | 2 | 4 | 1 | 1 | 2 | 2 | 20 | 6.41 |
| Tetralogy of Fallot | 0 | 0 | 3 | 1 | 3 | 2 | 2 | 1 | 2 | 3 | 17 | 5.45 |
| TGA | 5 | 3 | 2 | 1 | 2 | 1 | 2 | 0 | 0 | 0 | 16 | 5.13 |
| Pulmonary atresia | 1 | 2 | 1 | 1 | 2 | 1 | 0 | 0 | 1 | 1 | 10 | 3.21 |
| Complex | 3 | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 0 | 0 | 9 | 2.88 |
| Bicuspid aortic valve | 0 | 0 | 0 | 0 | 1 | 0 | 2 | 2 | 1 | 2 | 8 | 2.56 |
| Coarctation of aorta | 2 | 0 | 1 | 1 | 0 | 1 | 2 | 0 | 1 | 0 | 8 | 2.56 |
| Aortic stenosis | 0 | 0 | 0 | 1 | 1 | 0 | 3 | 0 | 1 | 1 | 7 | 2.24 |
| Tricuspid atresia | 1 | 1 | 1 | 0 | 1 | 0 | 1 | 0 | 1 | 0 | 6 | 1.92 |
| Single ventricle | 1 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 5 | 1.60 |
| AV canal defect | 0 | 0 | 1 | 0 | 1 | 1 | 0 | 1 | 1 | 0 | 5 | 1.60 |
| Ebstein anomaly | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | 4 | 1.28 |
| Mitral valve prolapse | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 2 | 4 | 1.28 |
| TAPVC | 0 | 1 | 1 | 0 | 1 | 0 | 1 | 0 | 0 | 0 | 4 | 1.28 |
| Dextrocardia | 0 | 0 | 0 | 1 | 0 | 0 | 1 | 0 | 1 | 0 | 3 | 0.96 |
| DORV | 1 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 2 | 0.64 |
| Truncus arteriosus | 1 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 2 | 0.64 |
| Hypoplastic left heart | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 0.64 |
| Total | 39 | 27 | 39 | 28 | 40 | 38 | 33 | 17 | 31 | 20 | 312 | |

*CHD* Congenital heart disease; *DORV* Double outlet right ventricle; *TAPVC* Total anomalous pulmonary venous connection; *TGA* Transposition of great arteries

**Table 2: Prevalence studies of congenital heart disease.**

| Author [ref.no] | Setting | Study population | Number studied | CHD per 1000 of study population |
|---|---|---|---|---|
| Shrestha *et al.* 1980 [17][a] | Community | 5–16 y | 34,198 | 3.2 |
| Gupta *et al.* 1992 [18][a] | Community | 6–16 y | 10,264 | 0.8 |
| Vashishtha *et al.* 1993 [19][a] | Community | 5–15 y | 8,449 | 5.2 |
| Khalil *et al.* 1994 [8][a] | Hospital | Live births | 10,940 | 3.9 |
| Thakur *et al.* 1995 [20][a] | Community | 5–16 y | 40,950 | 2.25 |
| Chadha *et al.* 2001 [21][a] | Community | <15 y | 11,883 | 4.2 |
| Smitha R *et al.* 2006 [16][a] | Hospital | 0–≥10 y | 74,589 | 10.65 |
| Kapoor *et al.* 2008 [15][a] | Hospital | <15 y | 10,641 | 26.4 |
| Misra *et al.* 2009 [14][a] | School | 5–15 y | 118,212 | 1.3 |
| Wren *et al.* 2001 [9] | Community | Live births | 377,310 | 5.2 |
| Subramanyan *et al.* 2000 [10] | Hospital | Live births | 139,707 | 7.1 |
| Samanek *et al.* 1999 [11] | Community | Live births | 816,569 | 6.16 |
| Robida *et al.* 1997 [12] | Hospital | Live births | 49,887 | 12.23 |
| Fixler *et al.* 1984 [13] | Community | Live births | 379,561 | 6.6 |
| Dilber D 2010 [22] | Community | Live births | 205,051 | 7.2 |
| Present study 2011 | Hospital | 0–18 y | 36,541 | 8.54 |

[a]Indian studies

## Discussion

Most of the studies done in the past report a birth prevalence of CHD of 4 to 12 children per 1000 live births [5–13]. The rates of occurrence of CHD in different reports vary because prevalence varies due to duration and intensity of case finding, sensitivity of the diagnostic methods used. The use of 2-D echocardiography has helped in diagnosing even very small defects and the reported prevalence rates have increased.

Prevalence also depends on the study population, the population based studies being the best. The few recent studies available from India have taken into consideration only particular groups *i.e.,* newborns, school children. The study by Khalil *et al.* [8] included 10964 hospital live births and observed the incidence of 3.9/1000 live births. Misra *et al.* [14] reported a prevalence of 1.3 per 1000 school children 5 to 15 y of age. The former may miss out on a large number of small VSD, Tetralogy of Fallot or ductus dependent lesions, which present a little later than at birth. It also fails to focus on the prevalence of CHD. The latter study automatically excludes all children with severe lesions who would be school dropouts. Kapoor *et al.* [15] reported a prevalence of 26.3 per 1000 patients aged 0 to 15 y at a tertiary corporate hospital. Hence, they do not present a true picture.

The authors' observation of prevalence of 8.54 per 1000 children should be more representative as compared to earlier studies, because we included children 0 to 18 y attending a tertiary care hospital that caters to all strata's of society and is the only referral hospital in the region with facilities to diagnose and manage CHD. Smitha *et al.* [16] have reported a prevalence of 10.65 per 1000 children at three hospitals of Mysore. Since a large number of births in India take place at home, mostly

**Table 3: Pattern of congenital heart diseases in literature.**

| Author [ref.no] | Study population | Pattern (individual CHD expressed as % of total cases) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | VSD | ASD | PDA | PS | CoA | TOF | TGA | PA | TA |
| Shrestha *et al.* [17][a] | 5–16 y | 30 | 23 | 11 | | | 4 | | | |
| Vashishtha *et al.* [19][a] | 5–15 y | 41 | 11 | 4 | | | 14 | | | |
| Thakur *et al.* [20][a] | 5–16 y | 32 | 38 | | | | | | | |
| Sharma *et al.* [25][a] | <12 y | 53 | 13 | 13 | | 8 | 3.2 | 2.2 | 6 | |
| Kapoor *et al.* [15][a] | <15 y | 21 | 19 | 14 | 3 | | 5 | 1 | | |
| Misra *et al.* [14][a] | 5–15 y | 40 | 18 | 2 | 8 | | | | | |
| Smitha R *et al.* [16][a] | 0–≥10 y | 40 | 19 | 9.5 | | | 13 | .6 | | |
| Amro K [26] | <14 y | 43.4 | 13.6 | 8.3 | 6.2 | 3.4 | 9.5 | 5.5 | | 3.6 |
| Abbag F *et al.* [27] | Children | 32.5 | 10.4 | 15.8 | 10.1 | 3.3 | 4.5 | 1.5 | | 1.5 |
| Present study | 0–18 y | 30.4 | 17.6 | 9.6 | 6.4 | 2.5 | 5.4 | 5.1 | 3.2 | 1.9 |

[a] *Indian studies*; *ASD* Atrial septal defect; *CHD* Congenital heart disease; *CoA* Coarctation of aorta; *PA* Pulmonary atresia; *TA* Tricuspid atresia; *TGA* Transposition of great arteries; *TOF* Tetralogy of Fallot; *VSD* Ventricular septal defect

unsupervised by a qualified doctor, hospital statistics are unlikely to be truly reflective [3]. The actual prevalence in community may be somewhat lower as there will be many children who did not need to attend the authors' institution during the study period. This highlights the pitfall in finding the prevalence of CHD by certain group based surveys, and the need and importance of the community based surveys. Such studies are nonexistent in India [3]. Some of the prevalence studies available from India and other countries are summarized in Table 2.

**The prevalence of CHD at a tertiary referral hospital in Uttarakhand, India is 8.54 per 1000 children. Diagnosis in most cases is delayed.**

The age at detection of CHD varies due to the normal hemodynamic alterations occurring after birth (fall in pulmonary vascular resistance, closure of PDA). Also many CHD's especially minor defects tend to be asymptomatic and hence missed unless specifically sought. Most authors agree that half of all cases of CHD are detected by 1 mo of age, three fourth by 3 mo and almost all by 3–4 y of age [8, 23, 24]. In present study only 21% of CHD cases were detected by 1 mo of age, 43% were detected during infancy and 68% by 6 y of age. Thus diagnosis was delayed beyond 6 y in 32% of cases. This delay in diagnosis can be explained by lack of awareness, health facilities and pediatric cardiac care programs in India [3].

Estimates of the frequency of specific lesions vary, depending on whether the data are drawn from infants or older children and whether the diagnosis is based on clinical, echocardiographic, catheterization, surgical, or postmortem studies [5]. The pattern from various countries is remarkably similar. Table 3 summarises the pattern of CHD observed in some of the comparative age group studies available in literature.

Ventricular septal defect (VSD) is the most common malformation, occurring in 25–30% of all patients with congenital heart disease [24]. The present observation of VSD accounting for 30.45% of CHD cases correlates well with the reported range of 21–53% in literature (Table 3).

Atrial septal defect was the second most common CHD, comprising 17.63%. This correlates well with the frequency of 10–23% reported in various Indian studies, but is higher than 6–8% reported from western countries [24].

Tetralogy of Fallot was the most common cyanotic CHD comprising 5.45%, correlating well with other studies [15, 17, 27].

An important observation from the present study is the increasing number of children with an unrecognized or uncorrected CHD, growing into adolescents and adults. Only 11 of 142 children (7.7%) had undergone definitive treatment in the study by Misra *et al.* [14]. Of the 312 children diagnosed with CHD, only 29(9.29%) underwent definitive treatment at the authors' institution during study period. However the number of children who after diagnosis underwent definitive treatment at other centers is not known.

Prevention of all cases of CHD is impossible as the cause of most congenital heart defects is unknown [24]. The best approach, therefore, is early identification and management of the problem. This may be achieved by increasing awareness and early evaluation of suspected cases. Many affected children do achieve cure or long-term palliation. Therefore knowledge of prevalence of CHD is important because it can assist in co-ordination of pediatric cardiology services and establishing advanced diagnostic and treatment facilities within a region.

The drawback of the present study is that being a hospital based study it does not reflect true community prevalence.

## Conclusions

The prevalence of CHD at a tertiary referral hospital in Uttarakhand, India is 8.54 per 1000 children. Diagnosis in most cases is delayed. Only one fifth cases were diagnosed in neonatal period with only 43% of cases being diagnosed during infancy. VSD (30.45%) and TOF (5.45%) are the most common acyanotic and cyanotic congenital heart defects respectively. In absence of a known cause, early diagnosis and treatment appears to be the best approach to minimize the morbidity and mortality attributed to CHD.

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**Contributions:** NKB: concept and study design, generation and interpretation of data, drafting and critical intellectual inputs; MD: generation and interpretation of data, drafting; RK, AP, AR: generation of data, drafting; BPK: concept and study design, critical intellectual inputs. All authors approved the final draft submitted for publication.

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*References available on request Healthcare.India@springer.com*

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# Myocardial Perfusion Imaging in Non-ischemic Cardiomyopathy

**Haren Patel[a], Shane Prejean[a], Ami E. Iskandrian[a], Fadi G. Hage[a,b]**

> A 63-year-old African-American man was referred for exercise SPECT myocardial perfusion imaging (MPI) for the evaluation of non-exertional chest pain of 2-3 months duration that had worsened recently (occurring almost daily).

A 63-year-old African-American man was referred for exercise SPECT myocardial perfusion imaging (MPI) for the evaluation of non-exertional chest pain of 2-3 months duration that had worsened recently (occurring almost daily). He carries the diagnosis of dilated, non-ischemic cardiomyopathy (NICM) with left ventricular (LV) dysfunction by gated SPECT-MPI and 2-dimensional echocardiography (images not shown). His medication list is shown in Table 1.

He exercised for 8:15 minutes using a standard Bruce protocol (Table 2) and stopped due to fatigue. The baseline electrocardiogram (ECG) demonstrated sinus bradycardia, 1st degree AV block, and left ventricular hypertrophy with QRS widening and repolarization abnormalities (Fig. 1).

The MPI SPECT images using Tc-99m sestamibi were abnormal showing a large area of ischemia (Fig. 2). Gated images showed LV dilatation and diffuse hypokinesis with LV ejection fraction (EF) of 27%. When compared to his MPI from 10 years earlier, the ischemia is new, but the LVEF was unchanged.

Coronary angiogram revealed only minimal atherosclerotic changes, but no lesion was > 50% diameter stenosis (Fig. 3).

**Table 1: Baseline medication list.**

| |
|---|
| Aspirin 81 mg daily |
| Furosemide 40 mg daily |
| Carvedilol 25 mg twice daily |
| Irbesartan 300 mg daily |
| Digoxin 0.25 mg daily |
| Atorvastatin 20 mg daily |
| Potassium Chloride 10 mEq daily |
| Spironolactone 50 mg daily |

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| Table 2: Exercise stress test data. | |
|---|---|
| Exercise time (mins) | 08:15 |
| Baseline HR (bpm) | 52 |
| Peak HR (bpm) | 109 |
| Percent of age-predicted maximum HR (%) | 69 |
| Baseline BP (mmHg) | 143/65 |
| Peak BP (mmHg) | 153/76 |
| Exercise capacity (METS) | 9.9 |
| Result | Non-diagnostic due to failure to achieve 85% of age-predicted maximal heart rate and baseline ST/T changes |

## Discussion

Determining whether heart failure is secondary to coronary artery disease (CAD) or due to one of the many causes of NICM is critical in the evaluation of patients with significant LV dysfunction. SPECT-MPI has proven useful in differentiating ischemic versus NICM in both chronic and new onset heart failure with a high sensitivity (87-96%) and negative predictive value (96%) [1, 2].

The SPECT-MPI pattern in ischemic cardiomyopathy is characterized by large perfusion defects due to scar, ischemia, and/or hibernation. On the other hand, most (2/3) of patients with dilated NICM have an almost normal perfusion pattern, but a dilated LV cavity with severe wall motion/thickening abnormalities. However, some patients (like our patient) with no obstructive CAD by coronary angiography may have perfusion abnormalities (either reversible, fixed, or both). In many situations, the pattern is diffuse and does not correspond to a given vascular territory, but in a few (like our patient) it does. Often the size of the perfusion abnormality is small compared to the degree of LV dysfunction [3]. It is important to exclude attenuation artifacts as a cause of such defects because attenuation is magnified in the presence of LV dilatation and wall motion abnormalities due to partial volume effect. In our patient, the defect was reversible which makes it unlikely due to attenuation.

Several studies document abnormalities in myocardial blood flow and metabolism (using positron emission tomography) in patients with dilated cardiomyopathy due to microvascular dysfunction and microinfarcts, and thus it is unwise to refer to the imaging results as false positives when compared to coronary angiography, especially when accompanied by typical symptoms of angina [4–6]. It may be that microvascular abnormalities play a role in

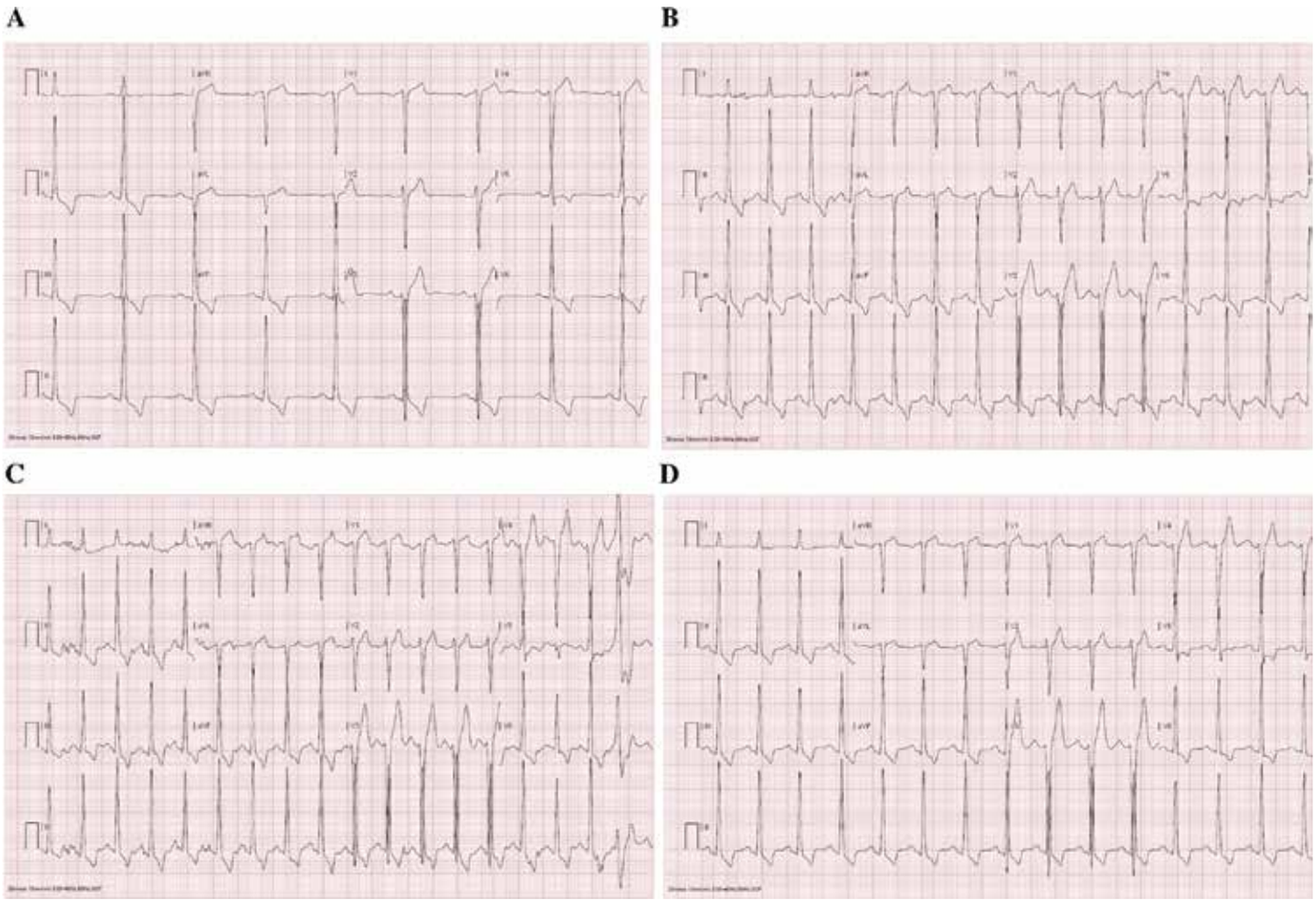


**Fig. 1:** The ECG at rest (**A**), early exercise (**B**), peak exercise (**C**), and recovery (**D**). Baseline ECG reveals sinus bradycardia, 1st degree AV block, and left ventricular hypertrophy with QRS widening and repolarization abnormality. There was no significant change in baseline ST-T wave abnormalities with exercise.

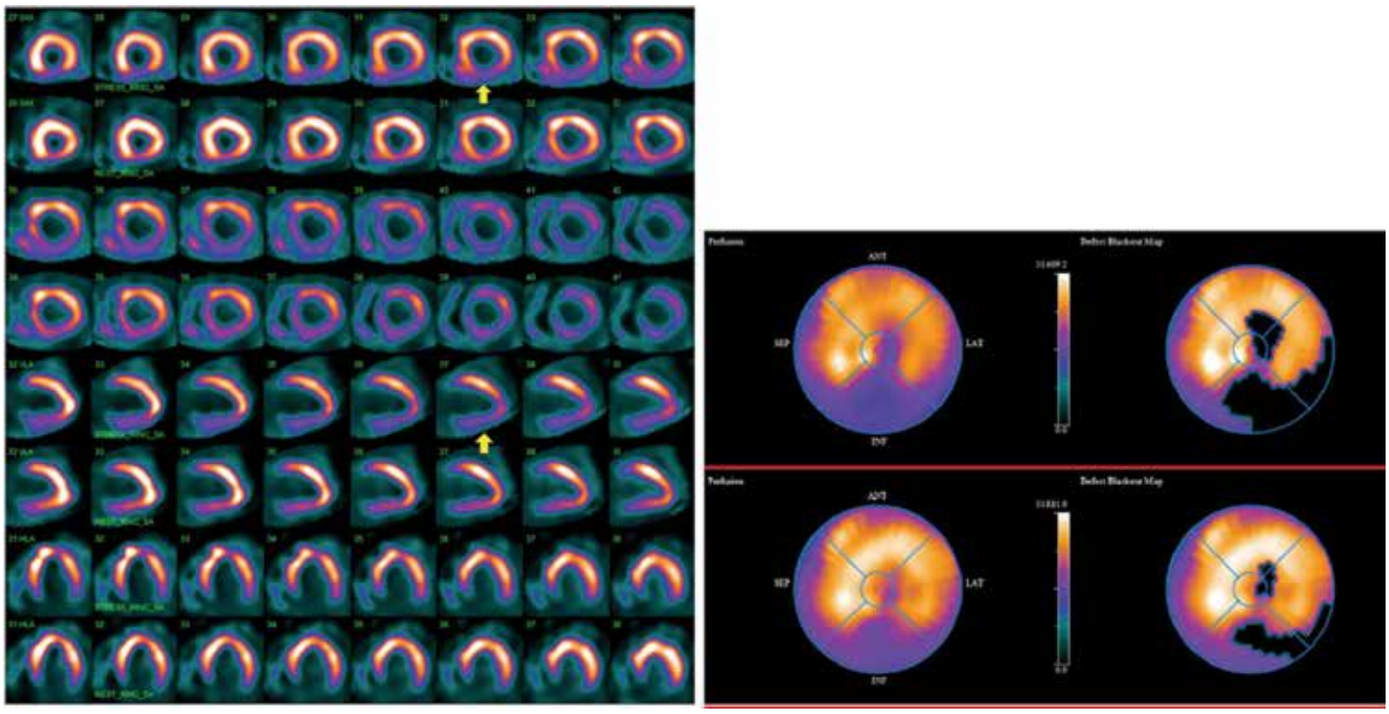

**Fig. 2:** *Left panel*: Stress/rest SPECT myocardial perfusion images (Tc-99m Sestamibi). There is a large area of mild partially reversible perfusion abnormality in the distribution of the left circumflex and right coronary arteries involving 25% of left ventricular myocardium (*yellow arrow*). There is no transient ischemic dilation, but there is severe fixed left ventricular dilation. *Right panel*: Raw and normalized polar maps at stress (*upper raw*) and rest (*lower raw*). The *blackened* areas represent perfusion defects.

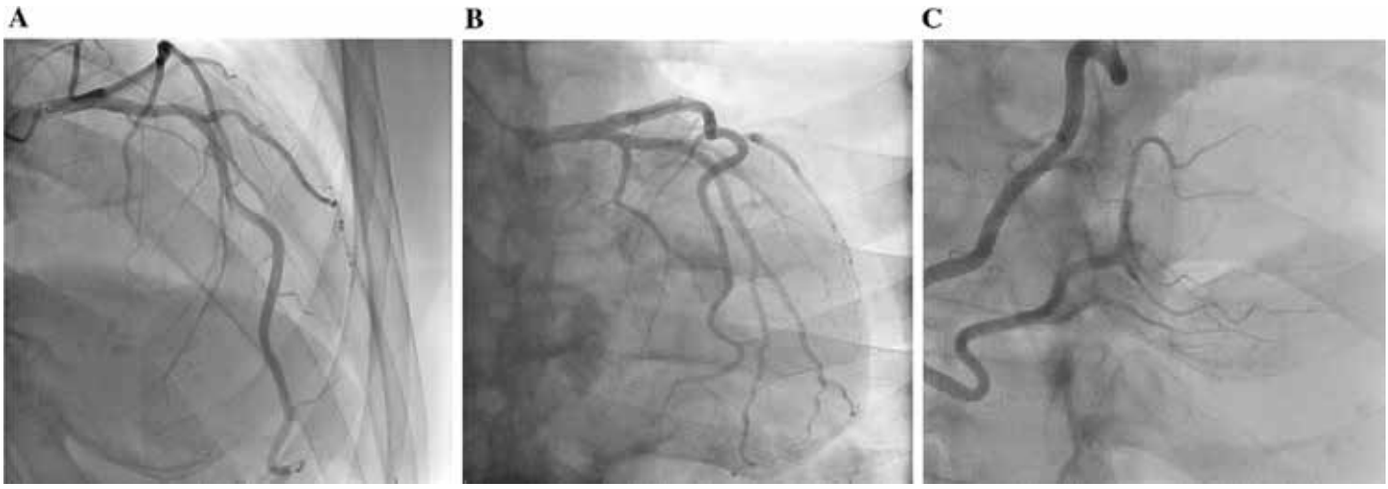


**Fig. 3: A** Left anterior descending artery in PA cranial projection. **B** Left circumflex artery in LAO caudal projection. **C** Right coronary artery in LAO cranial projection. *PA*, posteroanterior; *LAO*, left anterior-oblique

progression of the disease and symptoms (chest pain in our patient). Further, it is plausible that patients with NICM may develop CAD as they age, and therefore the development of new perfusion defects on serial imaging should not be disregarded. In this scenario, coronary angiography is not being performed to differentiate between ischemic vs. NICM, but rather to determine whether revascularization is an option to relieve symptoms. In the presented case, the symptoms were attributed to microvascular disease and medical therapy was intensified.

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# Multimodality Assessment of Ventricular Pseudoaneurysm After Non-reperfused Acute Myocardial Infarction

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Cardiac rupture is a frequent fatal mechanical complication of acute myocardial infarction [1]; in exceptional cases, the rupture of the left ventricle forms a pseudoaneurysm, which is characterized by the absence of myocardial tissue in its wall and a relatively narrow neck between the ventricle and the para-ventricular chamber [2].

A 72-year-old male, with cardiovascular risk factors (smoking, diabetes mellitus type II, age and sex) 2 months ago, had an acute myocardial infarction. He consulted a cardiologist who sent him to our institution for a myocardial perfusion study. The electrocardiogram showed QS pattern with negative inversion of T wave in DII, DII, and AVF (Fig. 1). The myocardial perfusion study demonstrated inferior transmural myocardial infarction, which extended as non-transmural to the inferolateral and inferoseptal walls, without ischemia (Fig. 2). The transthoracic two- and three-dimensional echocardiography demonstrated inferior-middle and apical wall akinesia and saccular pseudoaneurysm of 5.6 × 4.7 cm in the basal and middle

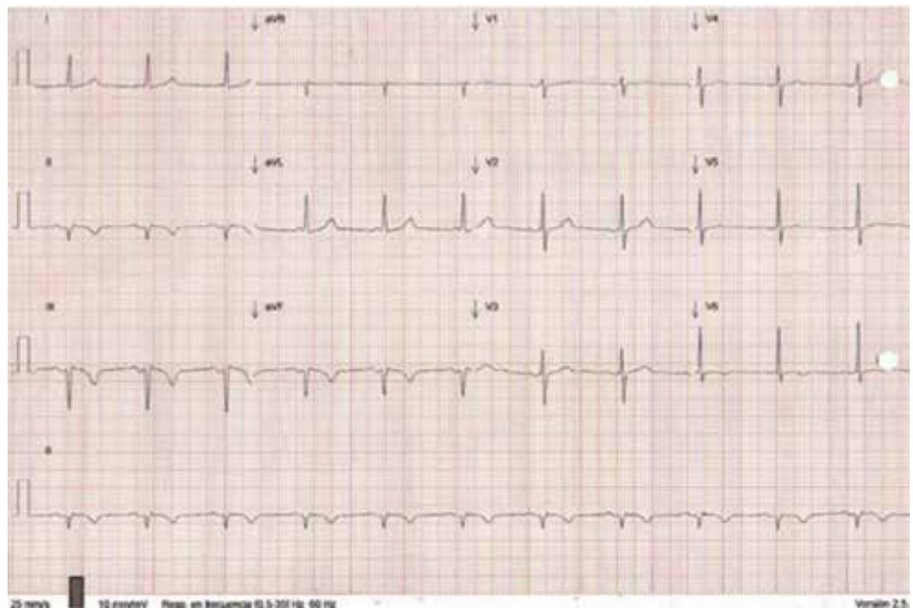

**Fig. 1:** Electrocardiogram in sinus rhythm with a heart rate of 75 bpm. QS pattern with negative inversion of T wave in DII, DII, and AVF is observed.

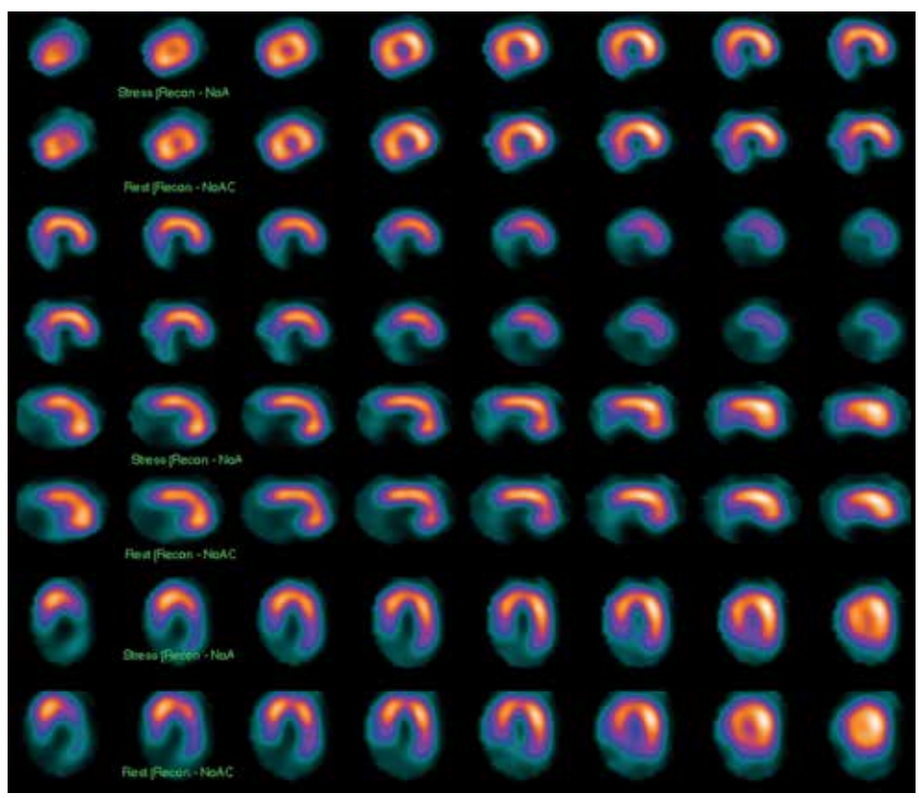


**Fig. 2:** $^{99m}$Tc-MIBI myocardial perfusion imaging (stress/rest) of the short-axis, vertical and horizontal long-axis views, showing an irreversible inferior defect without ischemia, which extended as non-transmural to the inferolateral and inferoseptal walls.

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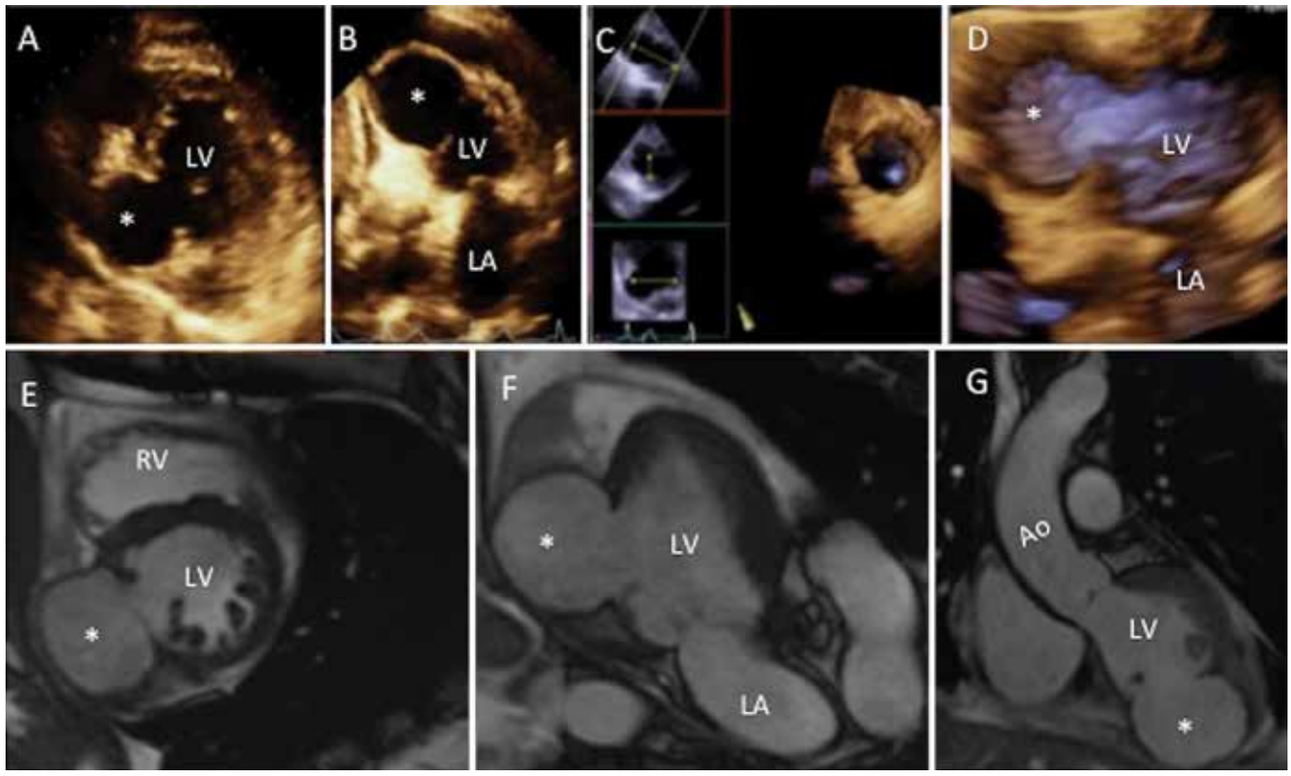


**Fig. 3:** Transthoracic 2D and 3D echocardiogram showing inferior-middle and apical wall akinesia and saccular pseudoaneurysm of 5.6 × 4.7 cm in the basal and middle segments of inferior and inferolateral walls, with entrance orifice of 2.6 × 2.4 cm and pericardial effusion **A, B, C, D**. MRI corroborated these findings, **E, F, G**. *Ao* aorta, *LA* left atrium, *LV* left ventricle, *RV* right ventricle

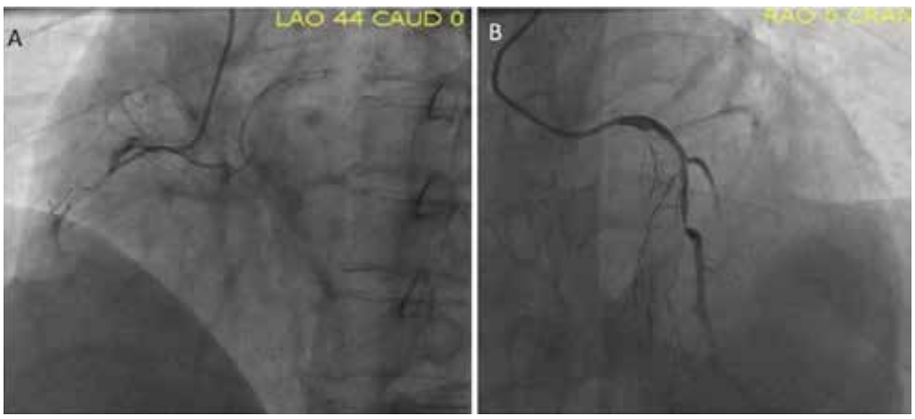


**Fig. 4:** Cardiac catheterization. (**A**) Left anterior oblique view showing total obstruction of the right coronary artery in its proximal segment. (**B**) In the right anterior oblique view, obstruction of 70% of the left anterior descending coronary artery in its proximal portion is visualized.

segments of inferior and inferolateral walls, with entrance orifice of 2.6 × 2.4 cm and pericardial effusion (Fig. 3A, B, C, D). The MRI revealed inferior myocardial infarction and the presence of pseudoaneurysm with laminar thrombus (Fig. 3E-G). The patient was hospitalized and the coronary angiography showed of 70% obstruction of the left anterior descending coronary artery in the proximal segment and chronic total obstruction of right coronary artery in its proximal segment (Fig. 4A, B). The patient underwent surgical left ventricular reconstruction with Dor's technique and coronary artery bypass grafting of the right and left anterior descending coronary arteries.

The evolution was satisfactory and he was under medical treatment with anti-platelets, beta-blocker, statins, and ECA inhibitors. At the 1 month of follow-up, he was in New York Heart Association functional class I.

The high suspicion index for its recognition, the emergent surgical intervention, and the stabilization made the patient's survival possible.

## Disclosure

Erick Alexanderson-Rosas, Oscar Mondaca-Garcia, Hector Zambrano-Guatibonza, Alondra Flores-Garcia, Isabel Carvajal-Juarez, Nilda Espinola-Zavaleta declare that there is no conflict of interest to disclose.

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# Masked Hypertension in CKD: Increased Prevalence and Risk for Cardiovascular and Renal Events

**Megha Babu[1], Paul Drawz[2]**

Hypertension and chronic kidney disease (CKD) are inextricably linked. The causal nature of the relationship is bidirectional. Patients with CKD are more likely to have high-risk hypertension phenotypes, such as masked and sustained hypertension, and are at increased risk for cardiovascular disease.

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Hypertension is a modifiable cardiovascular risk factor and has a bidirectional relationship with chronic kidney disease (CKD). CKD leads to hypertension through increased sodium retention, increased sympathetic tone, and endothelial dysfunction. As many as 86% of patients with CKD have hypertension [1, 2]. The impact of untreated hypertension on renal function is governed by a variety of factors, but can damage kidneys by causing glomerular sclerosis [3] and arteriolar nephrosclerosis [4]. Among CKD patients, higher systolic blood pressure (BP) has been shown to increase the risk of end-stage renal disease (ESRD), even after adjusting for other risk factors [5]. In fact, hypertension is a major risk factor for the development of chronic kidney disease (CKD) [6] and the second leading cause of ESRD in the U.S.A. [7].

The risk of cardiovascular disease associated with hypertension is higher among CKD patients [6, 8]. Maintaining target BP reduces the risk for cardiovascular events [9]. However, strict BP control does not delay the onset of ESRD [10]. The SPRINT demonstrated that targeting a systolic BP < 120 mmHg significantly reduced the risk of death and cardiovascular events when compared with a target of < 140 mmHg for non-diabetic adults. But among subjects

with CKD at baseline, there was no meaningful difference in the likelihood of experiencing significant deterioration in kidney function (a decrease in estimated glomerular filtration rate [eGFR] > 50%) or ESRD associated with the more intensive BP target [11]. However, it is worth noting that the SPRINT CKD population was at low risk for progression of CKD given the mild CKD at baseline (eGFR ~ 72 ml/min/1.73 $m^2$) and the low level of proteinuria (urine albumin to creatinine ratio of ~ 43 mg/g). Additionally, there was a greater masked effect in the intensive treatment arm than in the standard treatment arm when assessed by 24-h ambulatory BP monitoring (ABPM) [12]. These results demonstrate the masked hypertension may be of greater clinical significance when more aggressive clinic BP targets are utilized.

Recent reviews have described the factors and patient characteristics associated with increased prevalence of masked hypertension as well as the association between masked hypertension and adverse outcomes in the general population [13, 14]. Additionally, a recent editorial outlined the important knowledge gaps in diagnosing and managing masked hypertension [15]. In this review, we describe the increased prevalence of masked hypertension in patients with CKD and then describe the increased risk for target organ damage and adverse clinical events associated with masked hypertension in patients with CKD.

## Masked Hypertension

In clinical practice, a diagnosis of hypertension has typically been based on BP measurements in a clinic setting. The large majority of hypertension-related observational studies and nearly all randomized controlled trials have utilized clinic-based BP to define both hypertension and the target BP.

However, it is well known that several factors can influence manual BP readings and that clinic-based BPs reported in studies are a result of BP measurement techniques that do not adhere to recommended guidelines for measuring BP (Muntner, *JACC*, in press). As a result, patients who are otherwise normotensive may present with an elevated clinic-based BP ("white-coat" hypertension), while others who are, in fact, hypertensive can have clinic-based BPs within the normal range ("masked" hypertension). In order to "unmask" these phenomena, ambulatory blood pressure monitoring (ABPM) can be used to obtain out-of-office BP measurements throughout the day and night [16]. While ABPM is the preferred method for diagnosing masked hypertension because it provides an estimate of nighttime BP, home BP is an acceptable alternative [13]. The United States Preventative Services Task Force (USPSTF) and the 2017 ACC-AHA guidelines recommend out-of-office BP measurement to confirm the diagnosis of hypertension prior to treatment [17, 18••]. Interestingly, the USPSTF recommendation was based solely on the concern for over-treatment of white-coat hypertension and did not address the potential increased risk for adverse outcomes with masked hypertension that will be discussed in this review.

**Masked hypertension is associated with increased risk for target organ damage and adverse cardiovascular and renal outcomes in patients with CKD.**

Recommended thresholds for clinic and out-of-office BP for defining the various hypertension phenotypes are as follows:

1. Normal (or controlled hypertension) is defined by a clinic BP < 130/80 mmHg and either home BP < 130/80 mmHg or 24-h ABPM < 125/75 mmHg,
2. White coat hypertension is defined by a clinic BP ≥ 130/80 mmHg and either home BP < 130/80 mmHg or 24-h ABPM < 125/75 mmHg,
3. Masked hypertension is defined by a clinic BP < 130/80 mmHg and either home BP ≥ 130/80 mmHg or 24-h ABPM ≥ 125/75 mmHg,
4. Sustained hypertension is defined by a clinic BP ≥ 130/80 mmHg and either home BP ≥ 130/80 mmHg or 24-h ABPM ≥ 125/75 mmHg [18••].

## Increased Prevalence of Masked Hypertension in CKD

Masked hypertension is typically seen in about 8–20% of the general population who are not on antihypertensive therapy [19–22]. A meta-analysis of 36 studies incorporating 25,629 patients estimated the prevalence of masked hypertension to be about 19% among adults [23]. The prevalence of masked hypertension is likely higher in patients with CKD. Among 1492 participants with CKD in the Chronic Renal Insufficiency Cohort (CRIC) study, 28% had masked hypertension [24]. Similarly, in the Chronic Kidney Disease Japan Cohort (CKD-JAC), masked hypertension was present in 31% of participants [25]. In 617 participants from the African American Study of Kidney Disease and Hypertension (AASK) cohort, 25% had masked hypertension when defined by daytime ambulatory BP but as many as 43% had masked hypertension when both daytime and nighttime ambulatory BPs were considered [26]. It is worth noting that results are not entirely consistent; an earlier meta-analysis by Bangash and Agarwal found that only 8% of patients with CKD had masked hypertension [27]. Additionally, race and ethnicity may be associated with the prevalence of masked hypertension. In the International Database of Ambulatory BP in Renal Patients (I-DARE) study, when compared with CKD-JAC participants, those from AASK were more likely to have masked hypertension while participants from CRIC, Italy, and Spain were less likely to have masked hypertension [28]. In summary, the prevalence of masked hypertension is significant and likely greater in patients with CKD, although

prevalence estimates vary and can differ by patient characteristics.

## Masked Hypertension and Target Organ Damage

Studies of the general population reveal that masked hypertension is associated with increased cardiovascular target organ damage [21, 22, 29, 30]. Similar results have been observed in studies of patients with CKD. In the AASK cohort, participants with masked hypertension were more likely than those with normal BP and white-coat hypertension to have left ventricular hypertrophy (70% vs 54% and 50% in those with normal BP and white-coat hypertension, respectively) [26]. In the CRIC study, masked hypertension was associated with greater left ventricular mass index (2.52 g/m$^{2.7}$ higher, 95% CI 0.9 to 4.1) and pulse wave velocity (0.92 m/s higher, 95% CI 0.5 to 1.3) compared with those with controlled clinic and ambulatory BP [24]. In a cohort of patients with CKD from China, Tang *et al.* found that patients with masked hypertension were more likely to have left ventricular hypertrophy than those with normotension [31]. Masked hypertension is associated with cardiovascular target organ damage in patients with and without CKD.

In addition to cardiovascular target organ damage, masked hypertension is associated with greater proteinuria and reduced eGFR in the general population and in patients with CKD. Masked hypertension was associated with increased risk for CKD among 1023 residents in Ohasama, Japan [32]. In the AASK cohort, participants with masked hypertension were more likely than those with normal BP and white-coat hypertension to have a urinary protein:creatinine ratio > 0.22 mg/g [26]. In the CRIC study, masked hypertension was associated with lower eGFR and higher levels of proteinuria compared with those with controlled clinic and ambulatory BP [24]. Whether masked hypertension causes renal target organ damage or whether CKD leads to masked hypertension is difficult to ascertain. Patients with low eGFR and proteinuria are more likely to have a non-dipping pattern with elevated nighttime BP [33]. Additionally, a study of BP during and after exercise demonstrated that patients with masked uncontrolled hypertension and CKD had delayed recovery of exercise-induced hypertension compared with healthy controls [34]. In summary, masked hypertension is associated with renal target organ damage. Given the increased prevalence of masked hypertension in patients with CKD and the increased risk for cardiovascular disease in patients with CKD, future studies evaluating mechanisms underlying masked hypertension and treatment strategies targeting masked hypertension should focus on or at least include patients with CKD.

**The 2017 ACC-AHA guidelines recommend assessment of out-of-office BPs to detect masked hypertension and masked uncontrolled hypertension.**

## Masked Hypertension and Adverse Clinical Events

Masked hypertension is associated with cardiovascular and renal events as well as all-cause mortality. This has been demonstrated in a number of studies in the general population. Most recently, in an analysis of 63,910 Spanish patients with ABPM, compared with patients with normotension, risk for all-cause mortality was increased in those with masked hypertension (HR 2.83, 95% CI 2.12 to 3.79) and those with masked uncontrolled hypertension (HR 1.96, 95% CI 1.50 to 2.56). Similar results were observed for cardiovascular mortality [35••]. In the Jackson Heart Study, masked hypertension was present in 53% of participants and was associated with the development of CKD (adjusted OR 1.95, 95% CI 1.04 to 3.67) [36]. Fewer studies have evaluated the association between masked hypertension and adverse outcomes in patients with CKD. Kushiro *et al.* investigated the relationship between morning home systolic BP and clinic systolic BP and cardiovascular risk in hypertensive patients with or without CKD receiving olmesartan-based antihypertensive therapy using data from the HONEST study [37]. CKD patients were found to have a higher rate of cardiovascular events than non-CKD patients. Masked hypertension was associated with increased risk for a major cardiovascular event in patients with and without CKD [37].

Two studies have evaluated the association between masked hypertension and adverse clinical events in cohorts of patients with CKD. Minutolo *et al.* evaluated the association between masked hypertension and adverse clinical events in a cohort of 489 hypertensive patients with CKD. Fifteen percent of patients had masked hypertension. Over a median follow-up of 5.2 years, patients with masked hypertension were at increased risk for a cardiovascular composite of fatal and non-fatal myocardial infarction, congestive heart failure, stroke, revascularization, peripheral vascular disease, and non-traumatic amputation (HR 3.17, 95% CI 1.5 to 6.7) [38]. Patients with masked hypertension were also at increased risk for ESRD (HR 3.93, 95% CI 1.8 to 8.7) and all-cause mortality (HR 3.45, 95% CI 1.5 to 7.9) [38]. Similar results were observed in a cohort of CKD patients from China [39]. Compared with patients with normotension, patients with masked hypertension were at increased risk for all-cause mortality, renal events, and major adverse cardiovascular events [39].

While not specifically focused on masked hypertension per se, other studies of patients with CKD have evaluated the risk for adverse outcomes with elevated out-of-office BP after adjusting for clinic BP or in patients with controlled clinic BP. Home and clinic BPs were measured in a prospective cohort study of 217 veterans with CKD [5]. Over a median follow-up of 3.5 years, a one standard deviation increase in home systolic BP was associated with an increased risk for ESRD (HR 1.74, 95% CI 1.04 to 2.93)

in a model adjusting for clinic systolic BP and other risk factors. Similarly, elevated ambulatory BP was associated with increased risk for ESRD (HR 2.20, 95% CI 1.4 to 3.4) after adjusting for clinic systolic BP but the association was no longer significant after adjusting for other factors such as proteinuria and eGFR [40]. In the same cohort, 24-h ambulatory BP (HR 2.22, 95% CI 1.2 to 4.0) but neither clinic (HR 1.08, 95% CI 0.5 to 2.2) or home (HR 1.36, 95% CI 0.7 to 2.8) BP was associated with risk for cardiovascular outcomes [41]. In the AASK study, ambulatory and clinic systolic BP was associated with renal and cardiovascular events [42]. However, after controlling for clinic BP, elevated ambulatory BP was only associated with renal outcomes in participants with clinic systolic BP < 130 mmHg (interaction $P < 0.05$) [42]. These studies demonstrate that an elevated out-of-office BP is a risk factor for adverse renal and cardiovascular events in patients with CKD, independent of clinic BPs.

## Treatment of Masked Hypertension

The 2017 ACC-AHA guidelines recommend assessment of out-of-office BPs to detect masked hypertension and masked uncontrolled hypertension [18••]. This recommendation is based on the observational evidence of increased risk for adverse outcomes in these patients but does acknowledge, "there are no data on the risks and benefits of treating white coat and masked hypertension." Fortunately, there are ongoing trials evaluating whether treatment of masked hypertension is safe and effective. The MASTER (Masked Uncontrolled Hypertension Management Based on Office BP or on Out-of-Office [Ambulatory] BP Measurement) trial will enroll 1240 participants with masked uncontrolled hypertension and evaluate the effect of office or ambulatory BP based therapy on cardiac and renal target organ damage (ClinicalTrials.gov NCT02804074).

## Conclusions

Hypertension and CKD are inextricably linked. Not surprisingly, the prevalence of masked hypertension is increased in patients with CKD. Masked hypertension is associated with renal and cardiovascular target organ damage in patients with CKD. Additionally, while not as well established as in the general population, masked hypertension is associated with adverse cardiovascular and renal outcomes as well as increased risk for all-cause mortality in patients with CKD. Recent guidelines have stressed the importance of out-of-office BPs in the diagnosis and treatment of patients with hypertension. Future studies are needed to identify patients most likely to have elevated out-of-office BPs so that clinicians can appropriately target home and ambulatory BP monitoring to high-risk patients. Finally, randomized controlled trials are needed to determine whether masked hypertension is a modifiable risk factor.

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**Compliance with Ethical Standards**

**Conflict of Interest:** Megha Babu and Paul Drawz declare that they have no conflict of interest.

**Human and Animal Rights and Informed Consent:** This article does not contain any studies with human or animal subjects performed by any of the authors.

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# Acute Heart Failure: An Unmet Medical Need

Despite recent advances in the management of heart failure with reduced ejection fraction (HFrEF), the burden of acute heart failure (AHF) remains significant with a high morbidity and mortality that has not been improved by any treatment modality. A meta-analysis summarized the study results on the effects of tolvaptan on AHF, which failed to demonstrate an improvement in short-term and long-term mortality, length of hospital stay and reduced frequency of worsening heart failure (WHF). Similar trial results were also reported in other AHF studies, such as the ASCEND-HF and the RELAX-AHF-2 trials. In view of these inconclusive studies it is evident that improving the prognosis of AHF patients remains an unmet medical need. Further efforts should focus on organ damage protection, individualized treatment, patient benefits and standardized management programs, including immediate identification and management of cardiogenic shock and establishment of HF networks for close monitoring of AHF patients.

*Source: Rigopoulos, A.G., Bakogiannis, C., de Vecchis, R. et al. Herz (2019) 44: 53. https://doi.org/10.1007/s00059-017-4626-6. © Springer Medizin Verlag GmbH 2017.*

# Renal Artery Stenosis and Congestive Heart Failure: What do we Really Know?

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Congestive heart failure (CHF) is a major cause of morbidity, mortality, and health care expenditure. Although the role of renal artery stenosis (RAS) in CHF has been known, there are a number of areas of uncertainty.

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Congestive heart failure (CHF) and renal artery stenosis (RAS) are major causes of morbidity and mortality in the U.S.A. and global populations. CHF accounts for over 1 million hospitalizations per year [1]. RAS is prevalent among subjects with atherosclerotic disease such as coronary artery disease (CAD) or peripheral arterial disease (PAD) [2]. A relationship between RAS and flash pulmonary edema was reported by Pickering *et al.* in 1988 [3]. Pickering reported a case series of subjects with RAS and recurrent "flash pulmonary edema" and found that bilateral renal artery stenosis was highly prevalent in this group. Since that time, there have been significant investigations into the role of RAS and renal artery angioplasty or stent procedures for the treatment of renovascular hypertension [4, 5•]; however, the role of RAS in CHF has received less attention.

Intercommunication between the kidneys and the heart is critically important in people with CHF, and prior studies have demonstrated that renal function plays a critical role in predicting outcomes in patients with heart failure. Worsening renal function is a powerful predictor of adverse events among subjects with CHF [6]. In fact, impaired renal function is a better predictor of mortality in patients with advanced CHF than left ventricular ejection fraction [7]. However, with regard to RAS and CHF, there are many unanswered questions and much need for further research.

Multiple studies have demonstrated a high prevalence of RAS in subjects with CHF but the effect of RAS on CHF outcomes has been relatively

underexplored. A number of ongoing questions remain unanswered. Is RAS associated with intolerance to ACE-I/ARB/ARNI therapy in subjects with CHF? Is RAS associated with worsening renal function during treatment of acute CHF? Does the presence of RAS predict rehospitalization for acute CHF after an initial CHF hospitalization? What is the role of RAS in cardiorenal syndromes? Can renal artery stenting affect CHF outcomes among subjects with concomitant CHF and RAS? Is RAS equally prevalent among subjects with systolic versus diastolic CHF? The purpose of this review article is to summarize what is known and what is not known about RAS and CHF and highlight areas for future investigation.

## Underappreciated Prevalence of Concurrent RAS with CHF

Prior studies demonstrate that the RAS and CHF commonly coexist. MacDowall *et al.* found that 29/86 (34%) of subjects with CHF had concomitant RAS [8]. A more recent study of 366 subjects with heart failure showed that 112 (31%) had coexistent RAS (defined as > 50% stenosis on MRA). Of these 112 subjects with RAS and CHF, 37% had bilateral RAS [9]. A substudy of the EPOCARES clinical trial, which enrolled subjects with CHF and chronic kidney disease (CKD), found a 56.8% (21/37) prevalence of RAS (defined as > 50% stenosis on MRA). Of those 21 subjects with RAS, 8 (38%) were identified with bilateral RAS [10].

## Effect of RAS on CHF Prognosis

There are limited studies addressing the prognosis of subjects with concomitant RAS and CHF. A study by de Silva was one of the first to show that CHF patients with RAS had higher mortality rates than those without RAS, with mortality rates of 29% versus 10%, respectively [11]. This study used magnetic resonance angiography (MRA) and used a definition of > 50% stenosis to identify RAS. Out of the study cohort of 135 subjects with CHF, 54% had RAS with at least one renal artery having > 50% stenosis and 24% had bilateral RAS. Subjects with bilateral RAS also had significant worsening renal function over the 3-year follow-up period. There was a 17% reduction in mean eGFR in subjects with bilateral RAS compared with 1% decline in subjects without RAS and a 3% decline in subjects with unilateral RAS.

Bourantas *et al.* reported the largest cohort of subjects with CHF assessed for RAS [9]. A total of 366 subjects with CHF were assessed for RAS with MRA. RAS was present in 31% of the study subjects. Interestingly, among subjects with CHF and renal dysfunction (defined as eGFR < 60 mL/min/1.73 $m^2$), 95/366 (26%) had RAS. In a multivariate model, predictors of RAS in this cohort of CHF subjects included ischemic heart disease, declining renal function, and absence of treatment with ACE-I, ARB, or spironolactone. In the Kaplan–Meier analysis of long-term follow-up, RAS was associated with a higher risk of all-cause mortality (Fig. 1).

Interestingly, a prospective cohort study of 83 subjects with RAS assessed NT-proBNP at baseline and found that baseline NT-proBNP predicted long-term survival [12]. Among the subjects with CKD stages 1–3, elevated NT-proBNP had a HR of 3.63 for death. Among the subjects with CKD stages IV–V, the HR for death among subjects with elevated NT-proBNP was 8.30. Therefore, NT-proBNP may be a sensitive marker for cardiac involvement in subjects with RAS and a powerful prognostic factor among subjects with RAS.

Lastly, the RASHEF study was a retrospective cohort study of subjects hospitalized with CHF who also had renal duplex ultrasound performed [13•]. The presence of RAS was defined by duplex criteria as a renal-to-aortic ratio of ≥ 3.5, a peak renal artery systolic velocity of ≥ 200 cm/s, or a renal artery occlusion on ultrasound. The prevalence of RAS in this study was 15%. Among these subjects with CHF, the presence of RAS was associated with a higher mortality rate. By multivariate analysis, RAS was a significant predictor for all-cause death and cardiovascular death (hazard ratio [HR] = 4.2, 95% confidence interval [CI] 1.5–11.2, $P = 0.005$; and HR = 3.5, 95% CI 1.2–10.1, $P = 0.022$, respectively). In

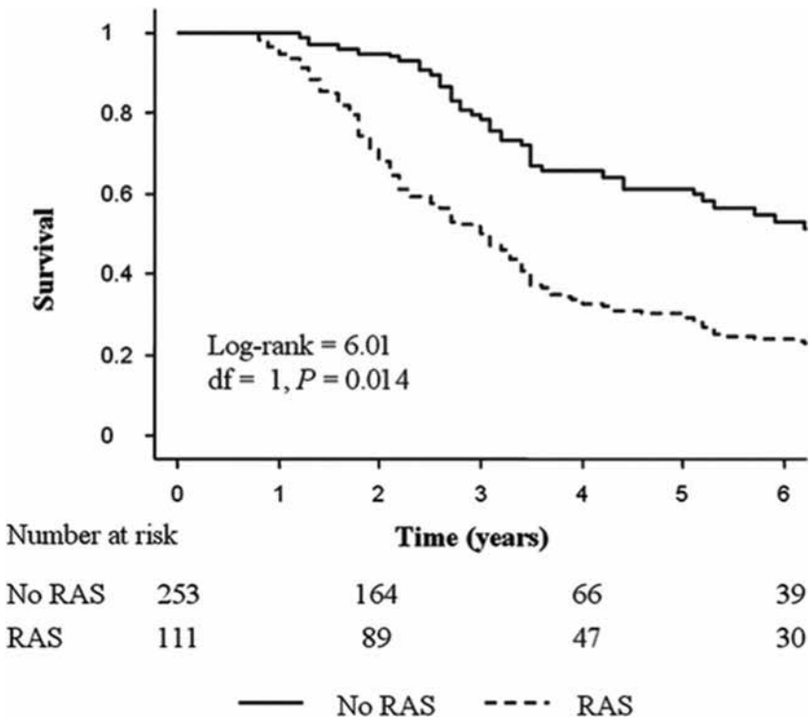


**Fig. 1:** The Kaplan–Meier plot showing survival for CHF patients with and without renal artery stenosis (RAS). (From Bourantas *et al.*, Copyright © 2012 John Wiley & Sons, Inc. Reprinted with permission) [9].

summary, RAS appears to be prevalent among subjects with CHF and is associated with adverse events during long-term follow-up, including all-cause mortality.

## Pathophysiology of Concomitant CHF and RAS

The physiology of the heart and kidneys is intricately interwoven and there are multiple signaling pathways by which the two organ systems communicate. These pathways include the sympathetic nervous system, renin-angiotensin-aldosterone (RAAS) system, and the natriuretic peptide system. All of these pathways are involved in CHF pathogenesis and are also affected by RAS.

Renal artery stenosis could have several implications for subjects with CHF. RAS may lead to decreased renal perfusion and GFR. The kidneys attempt to maintain renal perfusion with activation of the RAAS pathway and autoregulation of renal vasculature [14]. In patients with CHF, activation of RAAS has several negative consequences. Activation of renin leads to systemic vasoconstriction through the activation of the sympathetic nervous system (SNS) and via angiotensin II and aldosterone. Additionally, renin action leads to increased fluid retention. This exacerbates congestion in heart failure patients. In addition to short-term changes, there are also long-term changes in cardiac remodeling. Prior studies have demonstrated high rates of left ventricular hypertrophy among subjects with RAS [15].

Inhibition of the RAAS activation is typically achieved in CHF patients through the use of ACE-I, ARB, or now with ARNI. However, in patients with renal artery stenosis, this may lead to further decreased renal perfusion and may result in acute kidney injury in some patients with RAS. Intolerance to ACE-I/ARB/ARNI therapy and WRF during acute CHF are common clinical problems for heart failure patients. It is not known if subjects that cannot tolerate ACE-I/ARB/ARNI therapy have a higher prevalence of RAS, although Bourantas *et al.* did find that the absence of ACE-I, ARB, or spironolactone in their study of CHF subjects was an independent predictor of RAS [9]. In addition, the relation between RAS and worsening renal function during acute exacerbations of CHF is also not well described.

**The guidelines caution physicians on implementing revascularization unless RAS is identified as the suggested cause of hemodynamic instability in patients with CHF.**

## Renal Artery Stenosis and Acute CHF: The Vulnerable Phase

The susceptibility of ischemic kidney due to RAS may be exacerbated in acute CHF. The ischemic kidney may have altered renal perfusion and may activate adaptive mechanisms to maintain glomerular filtration rate. Subjects with acute CHF can experience an increase in renal venous pressure from baseline levels of approximately 5 mmHg up to 15–20 mmHg or higher in acute CHF. This increase in renal venous pressure can exacerbate worsening renal perfusion and the risk for acute kidney injury (AKI). In subjects with RAS, the ischemic kidney may be dealing with concomitant decreases in arterial perfusion due to the pressure loss in the renal artery. Such subjects may be particularly vulnerable to hemodynamic changes that occur with acute CHF, including both decreased cardiac output and increased renal venous pressure.

Worsening renal function during acute CHF has been classically associated with decreased cardiac output in CHF which leads to hypoperfusion of the kidney. However, more recent research indicates that this may not be the predominant hemodynamic factor leading to decreased renal function in acute CHF. Patients with acute CHF who developed worsening renal function did not have lower cardiac index levels compared with those without worsening renal function [16]. Research studies have suggested that the more predictive hemodynamic variable may be renal venous pressure and that right atrial pressure approximates renal venous pressure. Mullens *et al.* evaluated 145 people with acute decompensated heart failure for WRF. Elevated central venous pressure in patients with acute CHF was noted at both admission and follow-up. Patients who had a central venous pressure (CVP) of less than 8 mmHg were less likely to develop WRF. Additionally, CVP predicts the risk of WRF across the spectrums of other hemodynamic variables including cardiac index [16]. Another study observing the relationship among venous congestion and renal failure in patients with CHF found that there was an inverse relationship between the mean right atrial pressure and both renal plasma flow (RPF) and glomerular filtration rate (GFR) [17•]. Clearly, the hemodynamic effects of decompensated CHF on the kidney are complex. The specific hemodynamic effects of decompensated CHF on the ischemic kidney affected by RAS are even more complex and less studied. There is an unmet need for additional studies on the effects of RAS in patients with CHF. While there are many different variables at play, renal perfusion and renal venous pressure seem to have a large influence on predicting cardiorenal outcomes in subjects with CHF.

## Review of Treatment Guidelines

Treatment guidelines for RAS patients presenting with hypertension are now well established. The results of the Cardiovascular Outcomes in Renal Atherosclerotic Lesions (CORAL) randomized controlled trial demonstrated that among hypertensive patients, optimal medical therapy is equivalent to OMT plus renal artery stenting [4]. However, with regard to CHF, the American College of Cardiology and American Heart Association (ACC/AHA) guidelines regarding treatment

of RAS patients with CHF recommend that physicians proceed with caution due to the lack of randomized clinical trial data [18]. The ACC/AHA 2005 guidelines state that for CHF patients with hemodynamically significant RAS, the class I treatment is renal percutaneous revascularization. In conclusion, the guidelines caution physicians on implementing revascularization unless RAS is identified as the suggested cause of hemodynamic instability in patients with CHF. The ACC/AHA guidelines emphasize that the current data is based only on a few small prospective case series without large clinical trial data [18].

Small case series of subjects with CHF and RAS undergoing renal artery stenting have reported improved outcomes; however, these studies are limited by small sample size and their observational nature [19, 20]. There are no randomized controlled trial data on the effects of renal artery stenting among subjects with CHF and RAS.

As noted above, the CORAL trial showed that hypertensive RAS patients who underwent stenting, in addition to medical therapy, did not show improvement compared with those who were treated with optimal medical therapy alone [4]. The CORAL study had subjects with known CHF at baseline and others that developed CHF during the study follow-up. Further analysis may provide important insights about the interaction between RAS and CHF. These findings emphasize that additional studies are required to understand the optimal treatment for patients presenting with both RAS and CHF.

## Conclusion and Future Directions

There is an unmet need to determine the importance of RAS in contemporary management of CHF. The existing literature is limited in size and scope and thoroughness. Despite Pickering's description greater than 30 years ago, many important questions remain unanswered. Should diagnostic studies for RAS be pursued in subjects with CHF? If so, in which subgroups or which types of patient presentations? Given the frequency of CHF and RAS, these important issues deserve further investigation. Future studies must identify the prevalence of RAS in contemporary cohorts of subjects with HFrEF or HFpEF. The role of RAS in worsening renal function during acute CHF deserves further investigation.

**Compliance with Ethical Standards**

**Conflict of Interest:** Christopher J. Cooper was the PI for the CORAL study. In addition, Dr. Cooper has a pending patent on Thermomorph.

Rajesh Gupta, Mubbasher Syed, Nikita Ashcherkin, Katherine Chen, and Palavi P. Vaidya declare that they have no conflict of interest.

**Human and Animals Rights and Informed Consent:** All reported studies with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki Declaration and its amendments, institutional and national research committee standards, and institutional research guidelines).

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# Effects of Monoclonal Antibodies Against PCSK9 on Clinical Cardiovascular Events

The present meta-analysis was designed to improve statistical power and review the effects of monoclonal antibodies against PCSK9 on clinical cardiovascular events.

PubMed, Embase, Web of Science, and the Cochrane Library were searched from inception to May 2017. Studies considered to be eligible were randomized controlled trials about the effects of monoclonal antibodies against PCSK9 on clinical cardiovascular events. The primary endpoint was positively adjudicated cardiovascular events; the secondary endpoint comprised cardiac mortality, myocardial infarction (MI), coronary revascularization, stroke, and hospitalization for unstable angina.

The researchers included 20 randomized controlled trials involving 67,934 patients. Monoclonal antibodies against PCSK9 were associated with a significant reduction in positively adjudicated cardiovascular events (relative risk [RR] = 0.87; 95% confidence interval [CI] = 0.81–0.93; $z = 4.03$; $p = 0.000$), MI (RR = 0.78; 95% CI = 0.71–0.86; $z = 4.96$; $p = 0.000$), coronary revascularization (RR = 0.81, 95% CI = 0.75–0.88; $z = 4.93$; $p = 0.000$), and stroke (RR = 0.76, 95% CI = 0.65–0.89; $z = 3.47$; $p = 0.001$). Monoclonal antibodies against PCSK9 did not reduce hospitalization rates due to unstable angina. The results of subgroup analysis showed that evolocumab was associated with a lower risk of positively adjudicated cardiovascular events, MI, coronary revascularization, and stroke without reducing cardiac mortality. Alirocumab reduced the incidence of cardiac mortality but not of other cardiovascular events, while bococizumab was associated with a reduced risk of stroke.

Monoclonal antibodies against PCSK9 were associated with a lower risk of positively adjudicated cardiovascular events, MI, coronary revascularization, and stroke.

*Source: Zhu, Y., Shen, X., Jiang, Q. et al. Herz (2019) 44: 336. https://doi.org/10.1007/s00059-017-4640-8.* *© Springer Medizin Verlag GmbH 2017.*

# Coronary Artery Disease Risk Reclassification by a New Acoustic-based Score

To determine the potential of a non-invasive acoustic device (CADScor®System) to reclassify patients with intermediate pre-test probability (PTP) and clinically suspected stable coronary artery disease (CAD) into a low probability group thereby ruling out significant CAD. Audio recordings and clinical data from three studies were collected in a single database. In all studies, patients with a coronary CT angiography indicating CAD were referred to coronary angiography. Audio recordings of heart sounds were processed to construct a CAD-score. PTP was calculated using the updated Diamond-Forrester score and patients were classified according to the current ESC guidelines for stable CAD: low < 15%, intermediate 15–85% and high > 85% PTP. Intermediate

PTP patients were re-classified to low probability if the CAD-score was ≤ 20. Of 2245 patients, 212 (9.4%) had significant CAD confirmed by coronary angiography (≥ 50% diameter stenosis). The average CAD-score was higher in patients with significant CAD (38.4 ± 13.9) compared to the remaining patients (25.1 ± 13.8; p < 0.001). The reclassification increased the proportion of low PTP patients from 13.6% to 41.8%, reducing the proportion of intermediate PTP patients from 83.4% to 55.2%. Before reclassification 7 (3.1%) low PTP patients had CAD, whereas post-reclassification this number increased to 28 (4.0%) (p = 0.52). The net reclassification index was 0.209. Utilization of a low-cost acoustic device in patients with intermediate PTP could potentially reduce the number of patients referred for further testing, without a significant increase in the false negative rate, and thus improve the cost-effectiveness for patients with suspected stable CAD.

*Source: Schmidt, S.E., Winther, S., Larsen, B.S. et al. Int J Cardiovasc Imaging (2019). https://doi.org/10.1007/s10554-019-01662-1. © The Author(s) 2019.*

# Mesenchymal Stem Cell Therapy for Heart Failure: A Meta-analysis

Mesenchymal stem cell (MSC) treatment has emerged as an important adjunct therapy for heart failure. However, the use of MSC to treat heart failure has not been well established. We conducted a systematic review and meta-analysis to evaluate the efficacy of MSC treatment for heart failure.

PubMed, Embase, and the Cochrane Central Register of Controlled Trials were searched. Randomized controlled trials (RCTs) assessing the influence of MSC treatment on cardiac function in heart failure were included in this analysis. Two investigators independently searched the articles, extracted data, and assessed the quality of the included studies. Meta-analysis was performed using the fixed-effect model or random-effect model when appropriate.

Six RCTs involving 625 patients were included in the meta-analysis. Compared with control interventions in heart failure patients, MSC treatment had no significant influence on cardiovascular death (RR = 0.76; 95% CI = 0.38–1.52; $p = 0.43$); however, it was associated with significantly increased left ventricular ejection fraction (LVEF; mean = 9.64; 95% CI = 7.56–11.71; $p < 0.00001$) and reduced rehospitalization rate (RR = 0.41; 95% CI = 0.23–0.73; $p = 0.003$). In addition, no significant difference between the two groups was observed for the incidence of myocardial infarction (RR = 0.72; 95% CI = 0.10–5.02; $p = 0.74$), the recurrence of heart failure (RR = 0.88; 95% CI = 0.28–2.81; $p = 0.83$), and total death (RR = 0.68; 95% CI = 0.37–1.25; $p = 0.21$).

Although MSC treatment can significantly improve LVEF and reduce rehospitalization rates, it does not have a significant influence on cardiovascular death, myocardial infarction, heart failure, and total death.

*Source: Fu, H. & Chen, Q. Herz (2018). https://doi.org/10.1007/s00059-018-4762-7. © Springer Medizin Verlag GmbH, ein Teil von Springer Nature 2018.*

# Worldwide Dyslipidemia Guidelines

**Marcin Adam Bartlomiejczyk[1], Peter Penson[2], Maciej Banach[1,3]**

Despite the differences in statin intensities, safety concerns, use of risk estimators, or treatment of specific patient subgroups, there are more similarities than differences between the guidelines from both a clinical and practical point of view. Physicians ought to understand both similarities and differences in guideline recommendations to make the right decision regarding statin therapy for individual patients.

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The standard definition of clinical practice guidelines (CPGs) is "systematically developed statements to assist practitioners and patient decisions about appropriate health care for specific circumstances" [1]. CPGs are based on evidence, literature data, and medical principles [2]. Understanding the limitations of accessible evidence and an awareness of other available guidelines will support specialists to make personalized decisions with patients and improve the clinician–patient discussion [3, 4]. We need to create universal solutions for CPG on dyslipidemia to have guidelines that will simplify the decision-making process. In this paper, we consider five guidelines distributed by high-profile cardiovascular societies. From North America (American College of Cardiology/American Heart Association [ACC/AHA] [5••] and Canadian Cardiovascular Society [CCS] [6••]), Europe (European Society for Cardiology/European Atherosclerosis Society [ESC/EAS] [7••], Polish Lipid Association [PoLA] [8••], National Institute for Health and Care Excellence [NICE] [9••]), and Chinese guidelines [10••]. In the later sections of the article, we will try to indicate the differences in statin intensities, treatment of specific patient subgroups, use of risk estimators, and consideration of safety concerns. This will enable clinicians to understand these differences and similarities, in order to make the most appropriate choices with respect to lipid-lowering therapy.

Of note, the ACC/AHA plan to release updated lipid CPG in November 2018; at this time, it is uncertain whether the risk cut-points and treatment thresholds will differ from their prior 2013 guidelines, and whether they will re-incorporate a strategy of targeting to specific LDL-C reductions [11].

## Clinical Evidence in Guideline Recommendations and Risk Estimators

Guidelines are based on information from various sources. In preparing their guidelines, the ACC/AHA took into account only randomized control trials (RCTs) and their systematic reviews and meta-analysis. Additionally, studies of poor quality were rejected [5••]. In contrast, the ESC/EAS and CCS did not specify restrictions on the types of studies, but they applied rigorous analysis to published data and recommendations [6••, 7••]. Meanwhile, PoLA considered results obtained from research conducted with a random selection of participants in the general population and studies conducted in patients using primary care [8••]. Chinese guidelines were created on the basis of clinical and epidemiological studies on the Chinese population, which were combined with international research and guidelines [10••]. NICE guidelines were based on systematic reviews and RCTs [9••]. Each guideline describes the strength for every recommendation using recommendation classes (e.g., I, IIa, IIb, and III) and the quality of the evidence (e.g., levels of evidence from A to C) that supports them [6••, 7••, 8••, 9••, 10••].

All CPGs reviewed here recommend statins as a first-line drug therapy for primary prevention, although various estimators for a 10-year risk for atherosclerotic cardiovascular disease (ASCVD) events are advised. ACC/AHA Pooled Cohort Risk Equations are used by the ACC/AHA, while the Framingham Risk Score (FRS) is recommended by CCS [5••, 6••, 12, 13]. In terms of predicted outcomes, the FRS is the most comprehensive, predicting 10-year risk of coronary heart disease, peripheral artery disease, heart failure, or cerebrovascular events. The ACC/AHA Pooled Cohort Risk Equations are restrictive, predicting 10-year risk for a first hard ASCVD event, defined as coronary heart disease death, stroke, or nonfatal myocardial infarction (MI). In Europe, the Systematic Coronary Risk Evaluation (SCORE) estimator is recommended by the ESC/EAS, which has the strictest outcome by calculating the risk of only fatal events [7••]. The SCORE estimator is most specific, predicting 10-year risk of a first fatal atherosclerotic event, including stroke, MI, sudden cardiac death, or other occlusive arterial disease. PoLA uses updated risk assessment tables (created based on SCORE) tailored to the Polish population—Pol-SCORE

**All CPGs reviewed in this article recommend statins as a first-line drug therapy for primary prevention, although various estimators for a 10-year risk for ASCVD events are advised.**

2015 [8••]. NICE recommends the use of the QRISK2 risk assessment tool for people under 85 years of age for primary prevention or people with T2DM (type 2 diabetes mellitus). They do not recommend using QRISK2 in people with T1DM (type 1 diabetes mellitus), chronic kidney disease (CKD), pre-existing CVD, family burden of hypercholesterolemia, or other disorders of lipid metabolism. People over 40 years of age should be subjected to CVD risk assessment on an ongoing basis, based on data included in the primary care system relating to CVD risk factors [9••]. Meanwhile, China based on the 2007 Blood Lipid Guidelines recommendation suggests using the risk of developing "ischemic cardiovascular disease" [10••]. These differences in outcome measures are important when analyzing the differences in treatment thresholds between the guidelines. Risk estimators come from major studies and take into account predictors such as sex, age, high-density lipoprotein cholesterol (HDL-C), total cholesterol (TC), and systolic blood pressure. Nevertheless, diabetes, ethnicity, and treatment for hypertension are not universally taken into account in all CPGs, and therefore patient risk may be calculated differently depending on the estimators used.

## Common Aspects of Guidelines

Comparing all the CPGs discussed here reveals that there are more similarities than differences between them from a clinical and a practical point of view. Examples of similarities between the discussed CPGs are as follows: (1) the use of statins as the first-line medications; (2) a preference for evidence from RCTs, when it is available; (3) the importance of discussion with patients in order to improve outcomes through shared decision-making [14]—especially when limited evidence from RCTs is available; (4) the suggestion that nonpharmacological measures are employed to enhance the treatment of dyslipidemia despite the fact that there is often relatively little RCT evidence to support such approaches (The PREDIMED trial, being a notable exception [15]); (5) management based on cardiovascular (CV) global risk considering interactions among all present in each patient.

With regard to individual CV risk estimators, all the guidelines are limited by the poor predictive power of calculators. Another common feature of the CPGs discussed here is the categorization of statins by their efficiency into low-, medium-, and high-intensity classes. "Intensity" is the best way to classify statins in guidelines, because different medications in comparable doses may show different intensities as defined as the level of low-density lipoprotein cholesterol (LDL-C) reduction. They are characterized by their ability to reduce pretreatment

concentrations of LDL-C levels by < 30%, 30 to 40–50%, and > 40–50%, respectively. High-intensity statins should be used in patients with high LDL-C/non-high-density lipoprotein cholesterol (non-HDL-C) levels, which need to be reduced because of a high individual CV risk. An exception to this approach is found in the Chinese guidelines in which statins were divided into two intensity groups: medium and high. They are characterized by the ability to lower LDL-C levels by 25–50% and > 50%, respectively. Interestingly, there are also a lot of similarities in statin classification due to their effectiveness. However, there is not complete agreement between CPGs in this area. Table 1 illustrates the classification of statins by their ability to reduce plasma LDL-C levels. The CCS does not focus on statin intensity or dosing but rather on a targeted reduction in LDL-C level [6••]. ACC/AHA and NICE recommend statin dose or intensity based on clinical profiles [5••, 18]. Discrepancies in statin classifying result from the use of various bibliographies during the creation of guidelines [16, 19, 20]. All guidelines include effectiveness as a criterion in the choice of statins to use. NICE conclude that atorvastatin should be used in primary and secondary prevention at the dose of 20 and 80 mg/day, respectively.

## Primary Prevention

Statin treatment is recommended by ESC/EAS if the patient has a 10-year ASCVD risk of 5 to 10% using SCORE risk estimator and LDL-C ≥ 2.5 mmol/l (100 mg/dl) [7••]. The CCS suggest a threshold of ≥ 20% 10-year ASCVD risk (the higher one) because of using FRS estimator [6••]. Using the 2013 ACC/AHA Pooled Cohort Risk Equations, various CPGs in the U.S.A. have adopted differing thresholds of ≥ 7.5% (ACC/AHA), ≥ 10% (USPSTF), and ≥ 12% (VA/DoD) 10-year risk of ASCVD respectively [6••, 12, 13]. Whereas in Chinese guidelines, it is < 5%, 5–9%, and ≥ 9% 10-year risk of ASCVD for low, medium, and high risk, respectively [10••]. According to Pol-SCORE, PoLA have adopted a threshold of < 1%, 1–5%, ≥ 5–< 10%, and ≥ 10% for low, medium, high, and very high risk, respectively [8••].

Simultaneously, all CPGs recommend treatment for patients with LDL-C level ≥ 4.9 mmol/l (190 mg/dl). The guidelines emphasize the importance of lifestyle (e.g., avoiding smoking, reducing excessive weight, heart-healthy diets, and physical exercise) before and in combination with pharmacotherapy to reduce the risk of ASCVD. Moreover, in all guidelines, it is clearly stated that statins should be considered to be first-line medicines during pharmacological treatment. In primary prevention,

**Table 1: Classification of statins due to their ability to reduce LDL-C (daily dose).**

| | Low intensity | Medium intensity | High intensity |
|---|---|---|---|
| ACC/AHA [5••] | < 30% LDL-C reduction | 30–49%, LDL-C reduction | ≥ 50%, LDL-C reduction |
| | Fluv.: 20–40 mg, Lova.: 20 mg, Prav.: 10–20 mg, Simv.: 10 mg, Pita.: 1 mg | Fluv.: 40 mg, Fluv.: ex 80 mg, Prav.: 40–80 mg, Lova.: 40 mg, Simv.: 20–40 mg, Ator:. 10–20 mg, Rosu.: 5–10 mg, Pita.: 2–4 mg | Ator.: 80 mg, Rosu.: 20–40 mg |
| ESC/EAS [16, 17] | 20–30%, LDL-C reduction | 31–40%, LDL-C reduction | > 40%, LDL-C reduction |
| | Fluv.: 40 mg, Prav.: 20–40 mg, Lova.: 10–20 mg, Simv.: 10 mg | Fluv.: 80 mg, Lova.: 40–80 mg, Simv.: 20 mg, Ator.: 10 mg, Pita.: 1 mg | Ator.: 40 mg, Rosu.: 40 mg, Pita.: 2–4 mg |
| NICE [9••] | 20–30%, LDL-C reduction | 31–40%, LDL-C reduction | > 40%, LDL-C reduction |
| | Ator.: 20 mg, Fluv.: 20–40 mg, Prav.: 10–40 mg, Simv.: 10 mg | Fluv.: 80 mg, Simv.: 20–40 mg, Ator.: 10 mg, Rosu.: 5 mg | Simv.: 80 mg, Ator.: 20–80 mg, Rosu.: 10–40 mg |
| PoLA [8••] | < 50% LDL-C reduction | Min. 50%, LDL-C reduction | 50–60%, LDL-C reduction |
| | Simv.: 20–40 mg, Ator.: 10–20 mg, Rosu.: 5–10 mg | Ator.: 20–40 mg, Rosu.: 10–20 mg, Simv.: 20–40 mg + Ezet.: 10 mg, Ator.: 10–20 mg + Ezet.: 10 mg Rosu.: 5–10 mg + Ezet.: 10 mg, Ator.: 40 mg + Ezet.: 10 mg*, Rosu.: 20 mg + Ezet.: 10 mg* | Ator.: 40–80 mg, Rosu.: 20–40 mg, Simv.: 40 mg + Ezet.:10 mg, Ator.: 20 mg + Ezet.: 10 mg, Rosu.: 10 mg + Ezet.: 10 mg, Ator.: 40–80 mg + Ezet.: 10 mg**, Rosu.: 20–40 mg + Ezet.: 10 mg** |
| CCS [6••] | Does not focus on statin intensity or dosing but rather on a targeted reduction in LDL-C level | | |
| | Ator.: 10–80 mg, Fluv.: 20–80 mg, Lova.: 20–80 mg, Prav.: 10–40 mg, Rosu.: 5–40 mg, Simv.: 10–80 mg, | | |
| Chinese [10••] | No recommendations | 25–50%, LDL-C reduction | ≥ 50%, LDL-C reduction |
| | | Ator.: 10–20 mg, Rosu.: 5–10 mg, Fluv.: 80 mg, Lova.: 40 mg, Pita.: 2–4 mg, Prav.: 40 mg, Simv.: 20–40 mg, Xuez.: 1.2 g | Ator.: 40–80 mg*, Rosu.: 20 mg |

*ACC/AHA*, 2013 American College of Cardiology/American Heart Association Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults; *CCS*, 2016 Canadian Cardiovascular Society Guidelines for the Management of Dyslipidemia for the Prevention of Cardiovascular Disease in the Adult; *PoLA*, 2016 Polish Lipid Association; *ESC/EAS*, 2016 European Society for Cardiology/European Atherosclerosis Society Guidelines for the Management of Dyslipidemias; *NICE*, National Institute for Health and Care Excellence; *Ator.*, Atorvastatin; *Ezet.*, Ezetimibe; *Fluv.*, Fluvastatin; *Lova.*, Lovastatin; *Pita.*, Pitavastatin; *Prav.*, Pravastatin; *Rosu.*, Rosuvastatin; *Simv.*, Simvastatin; *Xuez.*, Xuezhikang; *ex*, extended release. * in the case of baseline LDL-C > 190 mg/dl (4.9 mmol/l) very intensive hypolipidemic therapy (LDL-C reduction > 60%), ** very intensive hypolipidemic therapy (LDL-C reduction > 60%)

all CPGs put great emphasis on joint decision-making and discussion between physicians and patients. Based upon the 10-year risk thresholds, the CPGs recommend different dosages and intensities of statins for primary prevention. The ACC/AHA guidelines indicate the use of high- or moderate-intensity statin therapy (for patients with ≥ 7.5% 10-year ASCVD risk). The ESC/EAS and CCS regulate the selection and dosing of statins by treatment goals [5••, 6••, 7••, 12, 13]. Interestingly, based on HPS2-THRIVE results, Chinese people may achieve lower LDL-C levels compared to Europeans when using the same drugs and dosing regimens [21]. Furthermore, higher doses do not affect the effectiveness of LDL-C lowering as demonstrated in the CHILLAS and DYSISCHINA studies [22, 23].

### Secondary Prevention

In secondary prevention, the ACC/AHA suggests variable intensities or doses of statins in patients with ASCVD. Patients over 75 years old without contraindications should receive high-intensity statins whereas others should obtain moderate-intensity statins [5••]. Meanwhile, ESC/EAS and CCS select the dose of statin based on therapeutic goals [6••, 7••]. All of the guidelines agree with each other that the main adverse effects (hepatitis, diabetes, and myopathy) have a marginally increased frequency of occurrence in statin-treated patients [24], but that benefits outweigh potential harms. Results from systematic reviews have shown that the true incidence of adverse effects is unknown and can be hard to measure. However, in general, the long-term safety profile of lipid-lowering therapy is good [8••, 9••, 10••, 25, 26]. Furthermore, all guidelines agree with each other that is a need of baseline and periodic analytical monitoring for early detection of adverse effects. On account of the low incidence of adverse effects, guidelines recommend monitoring only patients at risk or with clinical manifestation [27].

Future guidelines, such as the planned release of the 2018 ACC/AHA lipid guidelines, are likely to incorporate some recommendations for add-on therapies, including ezetimibe and/or PCSK9-inhibitors, for secondary prevention in patients who have not achieved the targeted LDL-C reduction on maximally tolerated statin doses.

### Monitoring Recommendations and Safety Concerns

Interestingly, the ESC/EAS guidelines state that a very important factor in counteracting liver and muscle damage is the ability to identify people at high risk. Risk factors include the following: small body size, advanced age, hepatic and renal dysfunction, female sex, multisystem disease, hypothyroidism, perioperative periods, and alcohol abuse [27, 28].

**The ESC/EAS guidelines state that a very important factor in counteracting liver and muscle damage is the ability to identify people at high risk.**

Similar risk factors are considered by the ACC/AHA guideline such as impaired hepatic or renal function, hemorrhagic stroke, Asian ancestry, age over 75 years, previous muscle disorders, or statin intolerance or simultaneous use of drugs affecting statin metabolism [29]. All discussed CPGs recommend monitoring of transaminases in each patient before starting treatment with statins. Moreover, monitoring of the biomarker creatine kinase (CK) is recommended by all of the discussed guidelines. ESC/EAS, PoLA, and Chinese guidelines recommend monitoring CK in all patients [7••, 8••, 10••, 12]. However, ACC/AHA [29] suggest baseline monitoring only in patients with muscular symptoms, and those at risk for myopathy (family or personal burden of muscle disease or statin intolerance or drug therapy which can increase the risk of myopathy).

NICE recommends checking CK before starting statin treatment only in some circumstances and after including assessment such as smoking status, blood pressure, alcohol consumption, body mass index (BMI), TC, non-HDL-C, HDL-C and triglycerides, HbA1c, renal function and eGFR (estimated glomerular filtration rate), transaminase level (alanine aminotransferase or aspartate aminotransferase), and thyroid stimulating hormone [18]. With respect to ongoing monitoring of therapy, the ACC/AHA guidelines [29] recommend measurement of CK and transaminases, only if symptoms occur, e.g., jaundice (suggesting hepatotoxicity) or symptoms suggesting myotoxicity (tenderness, cramping, pain, stiffness, general fatigue, or weakness). In the ESC/EAS, PoLA, and Chinese [8••, 27, 28] recommendations, it is stated that CK levels should be measured only if muscle symptoms occur after the initiation of statins. Unlike ACC/AHA guidelines [29], transaminases should be checked 8 weeks after starting statin therapy and once a year if its values are three times lower than normal value. NICE guidelines suggest that transaminases are always measured at baseline, and after the 3rd and 12th months of statin therapy [9••]. Liver and muscle damage, requiring cessation of therapy, are indicated by elevations of transaminase and CK to three and five times, respectively, the upper limit of normal.

The CPGs differ in their reasons for recommending the monitoring of lipid profiles. The ESC/EAS, Chinese, and PoLA [8••, 10••, 18, 27, 28] require plasma lipids to be measured, because they are the treatment targets. Lipid monitoring can also be useful in aiding and measuring compliance to lipid-lowering therapy. Coodley *et al.* have commented "A separate issue is the impact of regular lipid monitoring in promoting patient adherence to lifestyle changes or drug regimens that impact positively on their health, as found in a range of studies. It is unclear if only the process of monitoring is critical

in achieving this or a combination of education, regular contact, and adherence assessment" [17]. The 2013 ACC/AHA guidelines recommend monitoring to ensure that LDL-C level has decreased and to assess the therapeutic adherence of the treated person [29]. NICE also considers pharmacological adherence as a cornerstone of the management of CV risk but has not outlined any specific and effective specific strategies to increase the adherence to statin treatment [9••]. For ESC/EAS and PoLA guidelines, the elementary lipid profile includes TC (total cholesterol), TG (triglyceride), HDL-C, LDL-C, non-HDL-C, and TC/HDL-C ratio [8••, 27, 28]. ACC/AHA and NICE suggest TC, TG, HDL-C, LDL-C, and non-HDL-C [9••, 29]. NICE is unique in not recommending a fasting blood sample [9••]. Chinese guidelines not only recommend the measurement of TC, LDL-C, TG, and HDL-C but also include other blood lipids such as lipoprotein(a) and apolipoprotein (apo) A1 or B [10••]. All guidelines advise the periodic monitoring of analytical profiles after starting statin therapy. ACC/AHA guidelines recommend monitoring after 4–12 weeks of statin therapy and then every 3–12 months [29]. ESC/EAS recommend tests after 1–12 weeks of statin therapy, 3–4 weeks after changing medications, and once a year after reaching the therapeutic goal [27, 28]. NICE guidelines advise the determination of lipid profiles 3 months after starting lipid-lowering therapy and then once a year thereafter [9••]. In the case of acute coronary events, testing should be performed 4 weeks after initiation of lipid-lowering therapy. Interestingly, a meta-analysis performed by Perera *et al.* undermined the CPGs by showing that testing once a year is the most predictive as well as effective time period for monitoring lipids [30•].

## Special Groups of Patients

Special groups of patients include the elderly (age over 75 years old), who owing to the presence of various comorbidities and altered pharmacokinetic of drugs are at high risk of drug interactions. All of the CPGs discussed in this article highlight uncertainty around the use of statins in the elderly. The ACC/AHA does not contraindicate the use of statins if they are well tolerated, but at the same time does not recommend that they be initiated in primary prevention in this group. They also suggest that statins of moderate intensity should be used in secondary prevention [5••]. The ESC/EAS, PoLA, and Chinese guidelines suggest starting statin therapy for primary prevention if ASCVD risk is high. All guidelines recommend starting treatment with low-dose statins and then carefully increasing the dose until the target level of LDL-C (or target intensity of treatment) is reached [7••, 8••, 9••, 10••]. Furthermore, all CPGs highlight the importance of preventing cardiovascular diseases in the elderly by the promotion of a healthy lifestyle. Interestingly, Chinese guidelines recommended monitoring the kidney and liver function as well as CK in the elderly [10••]. Another special group of patients is people with kidney disease. The ACC/AHA does not make specific recommendations relating to the use of statins in patients with end-stage renal disease on maintenance hemodialysis [5••]. The CCS recommend that patients on dialysis should not initiate new statin therapy, but that they should continue existing statin therapy [6••]. On the other hand, according to PoLA, ESC/EAS, and Chinese guidelines, the decision should depend on the assessment of total cardiovascular risk based on the age of the patient and the degree of renal failure and/or estimated glomerular filtration rate (eGFR) [8••]. The KIDIGO guidelines (Kidney Disease: Improving Global Outcomes) determine the doses of optimal statins for individual stages of chronic renal failure, and not dependent on the LDL-C values. In this group of patients, medications excreted via hepatic metabolism (atorvastatin, fluvastatin, pitavastatin, ezetimibe) are preferred. Statins metabolized by CYP3A4 may lead to side effects due to multiple drug interactions and are not therefore recommended [8••].

**In secondary prevention, the ACC/AHA suggests variable intensities or doses of statins in patients with ASCVD.**

Another special group of patients is people with human immunodeficiency virus (HIV) and recipients of solid organ transplants. ESC/EAS and PoLA suggest caution with drug/drug interactions and suggest starting statin therapy with low doses and then gradually increasing. Both organizations recommend caution and clinical judgment before statin treatment is initiated in patients with inflammatory and rheumatologic diseases. Furthermore, they cite research showing that in palliative patients, discontinuation of statin therapy was not associated with deterioration in the assessment of cardiovascular parameters, including mortality; but significantly improved the quality of life of these patients [31]. Clinicians should always consider an individual approach to the patient, remembering that discontinuation of statin therapy might be associated with an increased risk of cardiovascular events [32, 33•]. Particular attention should be paid to the interaction of statins with protease inhibitors in patients with HIV due to metabolism by CYP3A4, leading to an increased risk of myopathy and rhabdomyolysis [7••]. While TC and LDL-C concentrations are often reduced in these patient groups, treatment may negatively affect the lipid profile. Highly active antiretroviral therapy (HAART), including primarily protease inhibitors, has a negative effect on the lipid profile, particularly on the development of atherogenic dyslipidemia [31]. If such lipid disorders are found, lipid-lowering medication may be considered as part of HAART, and pravastatin may be considered as recommended for HIV patients due to minimal metabolism

through the cytochrome P450 isoenzyme system. In addition to pravastatin, pitavastatin, atorvastatin, fluvastatin, and rosuvastatin may also be considered. It is also worth noting that the cardiovascular risk of a patient with HIV is higher than that of a patient without HIV (> 60%), and antiretroviral drugs, in particular protease inhibitors, increase this risk up to two-fold [8••]. ESC/EAS guidelines do not make any recommendations for people with psychiatric disorders as a barrier to drug compliance, owing to the lack of unambiguous data confirming the effectiveness of statin therapy in this population [5••, 7••].

### Issues to be Improved in CPG Regarding Lipids

Aside from the minor differences between guidelines, we can identify many common features in the various GCP recommendations. These can be implemented as a starting point for creating a common strategy. Consideration should be given to: (1) the need of treating global CV risk instead of individual risk factors; (2) the need to continue to gather clinical evidence to support the use of non-statin lipid-lowering drugs, (3) the need to gain confirmation from RCTs on nonpharmacological treatments for dyslipidemia.

Only the ESC/EAS in its guidelines mentions that "systematic comparison of current international guidelines to define areas of agreement and the reasons for discrepancies." [27, 28]. On the other hand, only NICE highlights the need for more data on effectiveness [9••]. There is a complete agreement on the need to obtain more data about the benefits of therapy, especially for older people, women, and diabetic patients. The main goal in the treatment of dyslipidemias is to avoid CV events. The use of non-HDL-C or LDL-C as targets or predictors of risk needs to be promoted without losing sight of the importance of managing global CV risk. Lipid parameters should be monitored, because clinicians make treatment decisions based on the numerical values of the results that distinguish healthy patients from ill patients. A reduction in global incidence of CV events could result from the effective implementation of evidence-based guidelines [34].

**NICE also considers pharmacological adherence as a cornerstone of the management of CV risk but has not outlined any specific and effective specific strategies to increase the adherence to statin treatment.**

## Conclusions

To sum up, there are more similarities than differences between the CPGs compared in this review, from both clinical and practical point of view. All of the CPGs recommend statins for primary and secondary prevention. Furthermore, they all recommend shared decision-making between the patient and the clinician. Taking all the similarities together, the recommended practical approach for the regular medical practice should be based on: (1) early detection of people with an increased CV risk (promoting the use of approved local risk-prediction tools); (2) strengthening the mainstream importance of nonpharmacological treatment for the reduction of CV Risk; (3) the need for global CV risk estimation and periodic monitoring of therapeutic response with analytical parameters (non-high-density lipoprotein cholesterol or low-density lipoprotein).

However, there are also differences between the guidelines, for example, in treatment of patients with comorbidities, statin intensity or in safety concerns. Moreover, using different risk estimators requires an understanding of compounding comorbidities and their impact on the occurrence of ASCVD. Globalization, technology development, and solutions (e.g., big data) will be useful in acquiring high-quality evidence on the basis of which it will be possible to develop better and better GCP. We hope that in the near future, we will succeed in developing consistent international guidelines.

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**Compliance with Ethical Standards**

**Conflict of Interest:** Maciej Banach has served on the speakers bureau of Abbott/Mylan, Abbott Vascular, Actavis, Akcea, Amgen, Biofarm, KRKA, MSD, Sanofi-Aventis, Servier, and Valeant and has served as a consultant to Abbott Vascular, Akcea, Amgen, Daichii Sankyo, Esperion, Lilly, MSD, Resverlogix, Sanofi-Aventis; grants from Sanofi and Valeant; Peter Penson owns four shares in AstraZeneca PLC and receives Speaker's fees from Amgen Inc.; Marcin A. Bartlomiejczyk has no conflicts of interest to disclosure.

**Human and Animal Rights and Informed Consent:** This article does not contain any studies with human or animal subjects performed by any of the authors.

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# Patient with Isolated Diurnal Hypertension

**Julian Segura**

A 70-year-old, Caucasian male, diagnosed of hypertension at 55 years of age, was referred by his family physician to perform a 24-h ambulatory blood pressure monitoring (ABPM) and to evaluate uncontrolled hypertension. He was treated with four antihypertensive drugs. A 24-h ABPM was performed, and the final diagnosis was uncontrolled diurnal hypertension.

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## Clinical Case Presentation

A 70-year-old, Caucasian male, diagnosed of hypertension at 55 years of age, was referred by his family physician to perform a 24-h ABPM and to evaluate uncontrolled hypertension. He was treated with enalapril 20 mg twice daily (one in the morning and one in the evening), hydrochlorothiazide 12.5 mg once daily (in the morning), amlodipine 5 mg once daily (in the evening) and bisoprolol 5 mg once daily. He is also receiving atorvastatin, aspirin and allopurinol.

### Family History

His mother and father were both hypertensives. He has one brother, also hypertensive.

### Clinical History

Coronary disease with stable angina, treated with coronary angioplasty and stenting 1 year before
Grade 2 obesity
Hypercholesterolemia treated with atorvastatin
Hyperuricemia treated with allopurinol

### Physical Examination

- Weight: 101 kg
- Height: 168 cm
- Body mass index (BMI): 35.8 kg/m$^2$
- Waist circumference: 112 cm
- Normal cardiopulmonary auscultation
- Abdomen without findings
- Extremities with palpable distal pulses, with minimal oedema

Repeated clinic BP and heart rate (HR) measurements were performed (Table 1).

### Haematological Profile

- Haematocrit: 49.5%
- Haemoglobin: 16.3 g/dL
- White blood cells: 7300/mm$^3$
- Platelets: 263,000/mm$^3$

### Blood Biochemistry

- Fasting plasma glucose: 93 mg/dL
- Fasting lipids: Total cholesterol 166 mg/dL, HDL-cholesterol 50 mg/dL, LDL-cholesterol 91 mg/dL, triglycerides 125 mg/dL
- Renal function: Creatinine 0.9 mg/dL, estimated glomerular filtration rate (MDRD formula) 88.7 mL/min/1.73 m$^2$
- Serum uric acid 6.1 mg/dL
- Electrolytes: Sodium 142 mEq/L, potassium 4.6 mEq/L
- Urine analysis: Albumin/creatinine ratio 6.7 mg/g
- Liver function tests: Normal
- Thyroid function tests: Normal

The ABPM performed shows insufficient BP control during the daytime period (Table 2 and Fig. 1).

### Diagnosis

Uncontrolled hypertension during daytime period

### Prescriptions

When reviewing the treatment with the patient, he tells us that the nocturnal dose of enalapril is sometimes forgotten. Thus, we decided to simplify the therapeutic regimen by reducing the number of pills. Enalapril, amlodipine and hydrochlorothiazide were discontinued and replaced by a fixed-dose combination of olmesartan/amlodipine/hydrochlorothiazide 40/5/12.5 mg administered once daily (in the morning). We also decided to perform a second ABPM 3 months later.

**Table 1: Repeated clinic BP and HR.**

| Systolic BP (mmHg) | Diastolic BP (mmHg) | HR (bpm) |
|---|---|---|
| 174 | 79 | 62 |
| 169 | 79 | 64 |
| 155 | 75 | 60 |

**Table 2: A 24-h ambulatory blood pressure monitoring.**

| | 24-h period | Daytime period | Night-time period |
|---|---|---|---|
| Systolic BP (mmHg) | 132 | 141 | 115 |
| Diastolic BP (mmHg) | 63 | 67 | 56 |
| HR (bpm) | 62 | 63 | 59 |

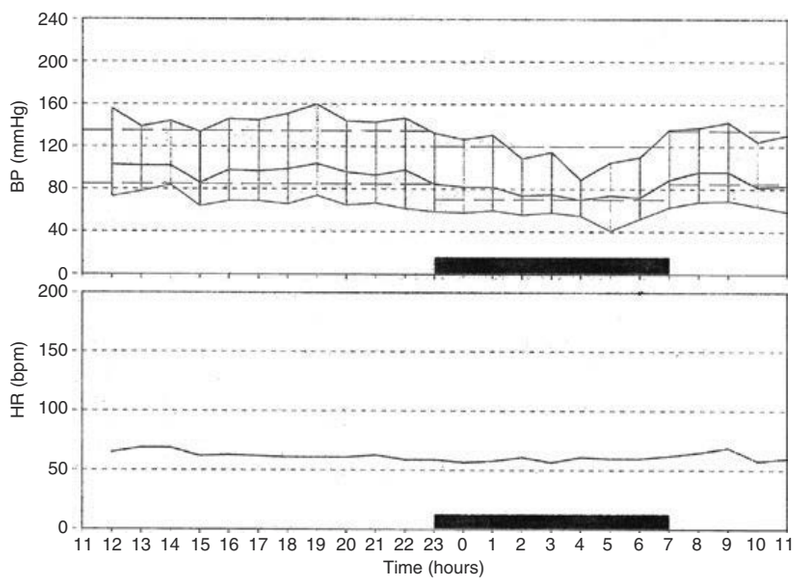


**Fig. 1:** A 24-h ambulatory blood pressure monitoring. *BP* arterial blood pressure, *HR* heart rate, *bpm* beats per minute, *Time (hours)*

## Follow-up (3 Months)

Repeated clinic BP and HR measurements were performed (Table 3).

Patient refers normal BP values at home. He also reports occasional dizziness at noon. ABPM shows a significant decrease in average BP levels during the daytime period (Table 4 and Fig. 2). For these reasons, we decided to withdraw the amlodipine and maintain olmesartan/hydrochlorothiazide 40/12.5 mg once daily (in the morning) and bisoprolol 5 mg once daily (at lunch).

## Discussion

There are several advantages of ABPM when compared with clinic BP assessment that reinforce a more widely use of this technique in a setting of clinical practice: ABPM gives many more BP measurements than conventional BP measurement, and individual BP is reflected more accurately by repeated measurements; ABPM also provides a BP profile away from the medical environment, thereby allowing the proper identification of individuals with a white-coat response or masked hypertension; ABPM can demonstrate a number of patterns of BP behaviour over the 24 h that may be relevant for the clinical practice of hypertension, such as nocturnal hypertension or increased BP variability; and by showing BP behaviour in different windows over a 24-h period, such as the white-coat and nocturnal periods, as well as the BP fluctuations triggered by environmental stimuli, it is possible to assess the efficacy of antihypertensive medication throughout the day and night rather than relying on a casual BP [1].

| Table 3: Repeated clinic BP and HR. | | |
|---|---|---|
| **Systolic BP (mmHg)** | **Diastolic BP (mmHg)** | **HR (bpm)** |
| 125 | 59 | 64 |
| 104 | 57 | 61 |
| 107 | 54 | 60 |

| Table 4: A 24-h ambulatory blood pressure monitoring. | | | |
|---|---|---|---|
| | **24-h period** | **Daytime period** | **Night-time period** |
| Systolic BP (mmHg) | 114 | 117 | 109 |
| Diastolic BP (mmHg) | 59 | 61 | 56 |
| HR (bpm) | 62 | 63 | 61 |

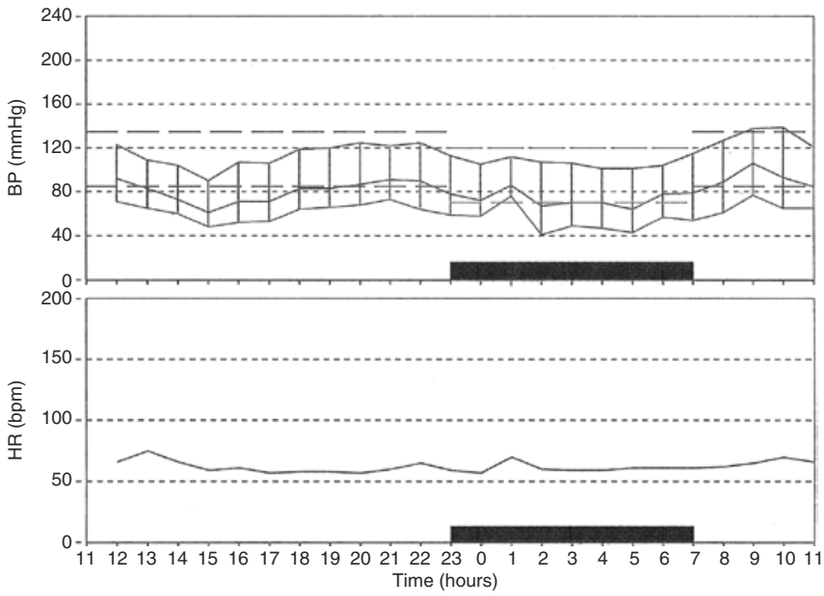


**Fig. 2:** A 24-h ambulatory blood pressure monitoring. *BP* arterial blood pressure, *HR* heart rate, *bpm* beats per minute, *Time (hours)*

**Among advantages of ABPM when compared with clinic BP, it should be noted:**

1. Ambulatory blood pressure monitoring gives many more measurements.
2. Ambulatory blood pressure monitoring provides a profile of BP away from the medical environment.
3. It is useful to assess the efficacy of antihypertensive medications.
4. All are correct.

Control of hypertension using ABPM out of medical consultations is much better than previously demonstrated by office-based surveys. Data from the Spanish ABPM Registry illustrate that according to the traditional view based on clinical BP, only 24% of hypertensive patients are controlled, a figure quite similar to that found in other European and some U.S. studies. Nevertheless, ABPM revealed that ambulatory BP control is higher than 50%. This conveys an encouraging message to clinicians, namely, that they are doing better than is usually thought [2]. Indeed, ABPM represents a useful tool not for only improving the diagnosis and management of hypertension but also for ensuring effective control of hypertension throughout the entire 24-h period, both during daytime and night-time [1].

The daytime window of ABPM is the period when the patient is away from the medical environment and engaged in usual activities. For almost all patients with hypertension, BP values during this window are lower than office or clinic BP [3, 4]. Systolic and diastolic hypertension is the commonest daytime pattern in patients aged less than 60 years [5]. ABPM should be performed in patients in whom BP tends to be unstable and highly variable at office BP or home BP measurements. Unstable BP may also be an important clue that antihypertensive treatment is ineffective. In this condition, ABPM may demonstrate both the efficacy of treatment and the smoothness of BP reduction [6]. BP evaluation out of the office using ABPM or self-home BP monitoring is now strongly recommended for the accurate diagnosis in many, if not all, cases with suspected hypertension. Moreover, there is evidence that the variability of BP might offer prognostic information that is independent of the average BP level [7].

**Threshold to diagnose diurnal hypertension is:**

1. Daytime BP ≥140/90 mmHg
2. Daytime BP ≥130/80 mmHg
3. Daytime BP ≥135/85 mmHg
4. Daytime BP ≥120/70 mmHg

Agreement between office- and ABPM-based methods of estimating BP control is poor. Physicians are, thus, prone to two types of bias when estimating BP control at the office, that is, false-negative (underestimation of BP control) and false-positive (overestimation). In public health terms, the magnitude is higher for the underestimation bias. ABPM uncovers a large portion of hypertensive patients (33.4%) whose BP control is not detected at the office. This office resistance represents the burden of 'clinically undetected control'. Likewise, ABPM uncovers a relatively small portion of hypertensive patients (5.4%) whose BP control is overestimated at the office. This isolated office control represents the burden of 'clinically undetected lack of control' [2].

**Select the incorrect sentence:**

1. Ambulatory blood pressure monitoring should be performed in patients in whom BP tends to be unstable and highly variable with office BP measurement.
2. Agreement between office- and ABPM-based methods of estimating BP control is poor.
3. Evaluation of blood pressure out of the office using ambulatory or self-home monitoring is strongly recommended for the accurate diagnosis.
4. Control of hypertension using ABPM outside medical settings is much lower than evidenced previously by office-based surveys.

The International Database of ABPM in relation to Cardiovascular Outcome (IDACO) determined ABPM thresholds corresponding to high BP on office measurement (>140/90 mmHg). Corresponding thresholds for hypertension with ABPM were 131.0/79.4 for 24 h, 138.2/86.4 for daytime and 119.5/70.8 mmHg for night-time periods [8]. Head *et al.* examined a different approach to derive age-related and sex-related ABPM equivalents to clinic BP thresholds for diagnosis and treatment of hypertension. They also compared clinic BP measurements taken by non-medically qualified health professionals with those taken by doctors, in order to assess whether a 'white-coat' effect might have influenced the findings of previous studies (which were based on doctor's measurements). This analysis provided a range of daytime ABPM measurements equivalent to recognized clinic BP thresholds [3]. Definitions of consensus for thresholds for hypertension diagnosis based on ambulatory blood pressure monitoring are 24-h average ≥130/80 mmHg, daytime average ≥135/85 mmHg and night-time average ≥120/70 mmHg [1, 9].

This case is a good example of the usefulness of the ABPM in the evaluation of the treated and uncontrolled hypertensive patient. The information provided by the ABPM allows adjusting the antihypertensive treatment based on the variability of blood pressure during 24 h, avoiding overtreatment or under-treatment.

### Take-home Messages

- There are several advantages of ABPM when compared with clinic BP that reinforce a more widely use in clinical practice.
- Ambulatory blood pressure monitoring gives many more measurements than conventional BP assessment, and individual BP is reflected more accurately by repeated measurements.
- Ambulatory blood pressure monitoring represents a useful tool not only for improving the diagnosis and management of hypertension but also for ensuring effective control of hypertension throughout the entire 24-h period, both during daytime and night-time.

*References available on request Healthcare.India@springer.com*

*Source: Segura J. (2019) Patient with Isolated Diurnal Hypertension. In: Hypertension and 24-hour Ambulatory Blood Pressure Monitoring. Practical Case Studies in Hypertension Management. Springer, Cham. https://doi.org/10.1007/978-3-030-02741-4_3.*
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## Development of New Antithrombotic Regimens for Patients with Acute Coronary Syndrome

Patients with acute coronary syndrome (ACS) require long-term antithrombotic intervention to reduce the risk of further ischemic events; dual antiplatelet therapy with a $P2Y_{12}$ inhibitor and acetylsalicylic acid (ASA) is the current standard of care. However, pivotal clinical trials report that patients receiving this treatment have a residual risk of approximately 10% for further ischemic events. The development of non-vitamin K antagonist oral anticoagulants (NOACs) has renewed interest in a 'dual pathway' strategy, targeting both the coagulation cascade and platelet component of thrombus formation. In the phase III ATLAS ACS 2 TIMI 51 trial, a 'triple therapy' approach (NOAC plus dual antiplatelet therapy) showed reduced ischemic events with rivaroxaban 2.5 mg twice daily, albeit at an increased risk of bleeding. Two studies have investigated the role of NOACs in combination with a $P2Y_{12}$ inhibitor, with or without ASA, in reducing bleeding risk in patients with atrial fibrillation undergoing percutaneous coronary intervention; two further studies are underway. Although these trials will help to inform optimal treatment protocols for secondary prevention of ACS, an individualized approach to treatment will be needed, taking account of the high frequency of co-morbid conditions found in this patient population.

*Source: George, S., Onwordi, E.N.C., Gamal, A. et al. Clin Drug Investig (2019) 39: 495. https://doi.org/10.1007/s40261-019-00769-6. https://doi.org/10.1007/s40261-019-00769-6.* *© The Author(s) 2019.*

# Pulmonary and Cardiac Drugs: Clinically Relevant Interactions

**H. Olschewski[1], M. Canepa[2], G. Kovacs[1]**

Chronic heart and lung diseases are very common in the elderly population. The combination of chronic heart failure and chronic obstructive pulmonary disease (COPD) is also common and, according to current guidelines, these patients should be treated for both diseases.

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Chronic heart disease and lung disease are both very common among people around 70 years of age. The most common single diagnosis in the former group is chronic heart failure and in the latter, chronic obstructive pulmonary disease (COPD). According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines, congestive heart failure is among the most important differential diagnoses of COPD [1] and vice versa. In patients with COPD, heart disease is associated with a poor prognosis [2, 3] and in patients with congestive heart failure, COPD is likewise associated with a poor prognosis [4]. Indeed, many patients suffer from both heart failure and COPD.

## Overlap of Heart and Lung Disease

According to the prospective ECLIPSE COPD cohort, nearly 10% of patients in the study had a known diagnosis of chronic heart failure and more than 25% had known "heart trouble" [2]. In a large NHS cohort from the UK with over 31,000 COPD patients and 150,000 matched controls, 17% of the COPD patients suffered from heart failure and 29% from ischemic heart disease [3]. These numbers, although impressive,

may still underestimate the problem. In The Netherlands, a cohort of about 400 COPD patients with no known heart disease underwent thorough multidisciplinary examinations in a specialized clinic. It was found that, based on echocardiography, 10% suffered from heart failure with reduced ejection fraction (HFrEF) and another 10% from heart failure with preserved ejection fraction (HFpEF; [5]). By far the highest rates of pathologic findings were found in patients over 75 years of age, both in males (mostly HFrEF) and females (mostly HFpEF). This suggests that at least 30% of COPD patients suffer from concomitant heart failure. And vice versa, when we look into large congestive heart failure cohorts, around 30% also suffer from COPD [4, 6, 7]. This means that the elderly population in developed countries presents with a broad overlap of congestive heart failure and COPD.

There have been several approaches to explain these strong associations, ranging from shared risk factors like smoking, to shared pathologic mechanisms like systemic inflammation, to shared genetic factors. The most comprehensive concept, however, was delivered by an American Thoracic Society (ATS)/European Respiratory Society (ERS) Task Force report, interpreting COPD "as the pulmonary component of a chronic multimorbidity." This concept explains why COPD is associated with many common risk factors, such as smoking, pollution, ageing, inactivity, and diet [8]. This also implies that COPD and congestive heart failure are not only very common in the adult population but also often combined in a single subject, i.e., COPD can be considered as a risk factor for congestive heart failure and vice versa. In addition, the Copenhagen City Heart Study showed that COPD also represents a strong risk factor for atrial fibrillation and a moderate risk factor for systemic arterial hypertension [9]. This was confirmed in the most recent large NHS cohort [3].

## Beta-adrenergic Receptor: Important Pharmacologic Target for Congestive Heart Failure and COPD

In congestive heart failure patients, beta-blockers are one of the most important therapeutic options because they significantly improve morbidity and mortality [10]. By contrast, COPD patients profit from beta-sympathomimetics, drugs that have been shown to improve lung function, dyspnea, and quality of life [11]. This may sound like a contradiction: How should we then treat patients who suffer from both COPD and congestive heart failure?

**In congestive heart failure patients, beta-blockers are one of the most important therapeutic options because they significantly improve morbidity and mortality.**

For COPD patients, the GOLD guidelines [11] and the ERS recommendations [12] provide a clear statement: "Comorbidities should be treated as if the patient did not have COPD."

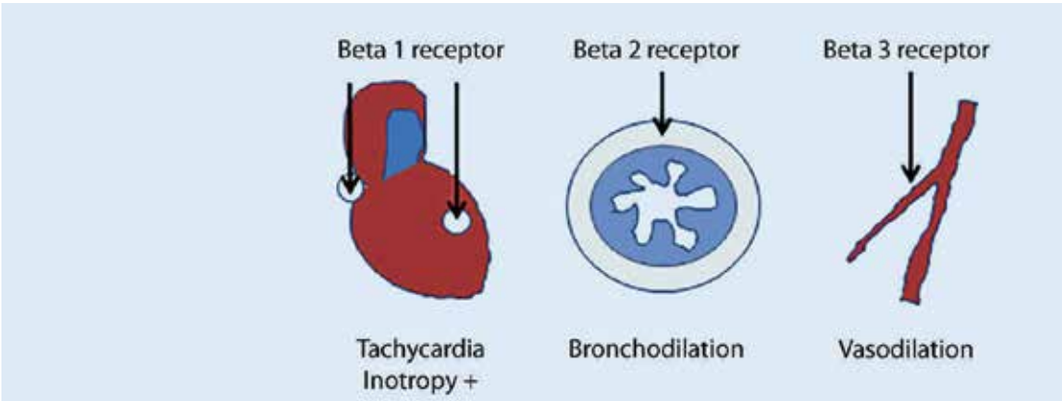
In cases of obstructive lung diseases, beta-sympathomimetics (LABA) are approved for COPD and asthma and they are recommended by the current guidelines for COPD [13] and asthma [14] although there is no evidence for a beneficial effect on mortality. Most of the evidence has been generated for combination treatments: for asthma with inhaled corticosteroids (ICS-LABA), and for COPD with long-acting muscarinic antagonists (LAMA-LABA). According to the GOLD and the ERS guidelines, these medications can be prescribed for symptomatic COPD patients even if significant heart disease is present.

In cases of congestive heart failure as a comorbidity of COPD, the GOLD/ERS recommendation [11, 12] means that patients with an indication for a beta-blocker should indeed receive a beta-blocker. According to the current guidelines for acute and chronic heart failure [10] and the Global Initiative for Asthma (GINA) guidelines for asthma [14], even asthma is not an absolute contraindication for beta-blockers, despite reports of adverse effects from the 1980s and 1990s with mostly unselective beta-blockers at high initial doses in patients with severe asthma. For patients with ischemic heart disease [15, 16] and with heart failure [17], beta-blocker use was associated with a significant beneficial effect on mortality. This was not only true for the whole study population but particularly for the subgroup of patients with concomitant COPD. In addition, beta-blockers are important medications for controlling atrial fibrillation and systemic hypertension.

## Receptor Specificity and Route of Application

### Beta-blockers

Cardiovascular diseases are the most frequent and important comorbidities of COPD and include ischemic heart disease, congestive heart failure, and atrial fibrillation. For these diseases there are clear indications for beta-blockers. In COPD patients, $beta_1$ selective beta-blockers are considered to be advantageous, although there are also data for the unselective $beta_1$/$beta_2$ adrenergic blocker carvedilol suggesting a good tolerability in COPD patients [18]. Still, a potential problem is the large overlap between COPD and asthma. Up to 30% of COPD patients may suffer from asthma as a comorbidity [19] and asthma patients may develop adverse effects from nonselective beta-blockers. If the $beta_1$/$beta_2$ effect of propranolol was 1, bisoprolol would have a ratio of 103 and nebivolol of 321 [20]. Nebivolol is a substance that has strong $beta_1$-blocking properties, virtually no effect on the $beta_2$ receptor and at the same time is a $beta_3$ receptor agonist (Fig. 1). This profile might be particularly




| | Beta 1 | Beta 2 | Beta 3 |
|---|---|---|---|
| Propranolol | -- | -- | -- |
| Carvedilol | -- | -- | ? |
| Metoprolol | -- | (-) | (-) |
| Bisoprolol | -- | (-) | (-) |
| Nebivolol | -- | (+) | (+) |

**Fig. 1:** Beta receptors, their main function in cardiovascular and pulmonary physiology, and the most important beta-blockers for clinical use.

advantageous for patients with heart disease and COPD with an asthmatic component and/or pulmonary arterial vasoconstriction. However, because there was no significant beneficial effect of nebivolol on mortality in a recent study with Asian patients [21], nebivolol was not recommended by all guidelines for chronic heart failure.

### Beta-sympathomimetics

Beta-sympathomimetics improve lung function and dyspnea by means of their bronchodilating properties via activation of the $beta_2$ receptor of the bronchial smooth muscle cells (Fig. 1). Principally they can be delivered systemically or via the inhaled route. Unfortunately, none of the available $beta_2$ agonists is highly selective for the $beta_2$ receptor and they all may cause $beta_1$ agonistic effects like tachycardia and increased oxygen demand of the heart. Therefore, systemic application, which is associated with many more cardiac side effects than inhaled application, is not recommended. In addition, the approved substances have different pharmacologic profiles. The short-acting $beta_2$ agonists (SABA), like salbutamol and fenoterol, were the first available substances, followed by long-acting $beta_2$ agonists (LABA) like salmeterol for twice daily use and ultra-long-acting substances like indacaterol, olodaterol, and vilanterol for once daily use. As a rule, immediate onset of bronchodilatation is associated with a short duration, and a slow onset with a long duration of the drug. However, there is one exception to the rule: Formoterol has both a rapid onset and a long duration of bronchodilation. This is why the GINA guidelines recommend only formoterol as an on-demand combination drug in Step 1 and steps 3–5 of asthma therapy [14]. Although there is no head-to-head comparison, LABA are considered superior to SABA for chronic stable asthma and COPD disease, because they are less prone to causing tachycardia and other cardiac side effects.

## Advantages of Combined Beta-blocker Plus Beta-sympathomimetic Therapy

When the patient is treated with an unselective beta-blocker, a concomitant LABA therapy may ameliorate any bronchoconstrictive effects. And vice versa, any adverse effects of the LABA on the heart will be ameliorated by the beta-blocker. When the patient is treated with a $beta_1$ selective beta-blocker, even a high-dose beta-blocker will not cause bronchoconstriction, because the beta receptors are stimulated by the LABA. And vice versa, as the LABA is delivered via the inhaled route, it will not cause major cardiac side effects and any minor side effects will be ameliorated by the beta-blocker.

In summary there is an excellent rationale for treating patients suffering from heart failure and COPD with both a $beta_1$ selective beta-blocker and an inhaled long-acting or ultra-long-acting $beta_2$ agonist.

## Potential Interactions Between Cardiac Medications and COPD

Aspirin is a mainstay of secondary prevention in ischemic heart disease. In addition, it has a significant preventive role for recurrent venous thromboembolism [22]. Aspirin increases the risk of bleeding and this

may affect COPD patients more than other patients owing to coughing, osteoporosis, and fragile small vessels. In addition, COPD may be associated with asthma and among these patients some will be sensitive to aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs). This special asthma phenotype is often associated with "late-onset asthma" and nasal polyposis. However, since the aspirin for ischemic diseases is taken on a daily basis, there will be a desensitization of the asthma mechanism and adverse effects on the airways are very unlikely.

Oral anticoagulants are often indicated in ischemic and congestive heart disease and in atrial fibrillation. Patients with COPD may be more prone to bleeding complications than patients without COPD. This is very obvious in the skin but also affects the abdominal muscles and other organs. Severe coughing in combination with osteoporosis represents a strong risk factor for rib and vertebral fractures. In such cases, anticoagulation may cause significant complications.

Amiodarone is still the most potent anti-arrhythmic drug and is used for ventricular and supraventricular arrhythmia. Unfortunately, there is a dose-dependent toxicity that can affect many organs. In the lung it causes alveolitis, which is associated with worsening of pulmonary gas exchange and severe hypoxemia. Because of the extremely long half-life of amiodarone, it may take many weeks after cessation of amiodarone treatment until the alveolitis improves. The risk of life-threatening complications of alveolitis is increased in subjects with pre-existing lung disease like COPD.

Angiotensin-converting enzyme (ACE) inhibitors (ACEi) remain important drugs for the treatment of congestive heart failure. However, they may frequently cause chronic cough and rarely they may cause angioedema. In COPD patients, cough is common and ACEi-induced cough may be mistaken for COPD or asthma exacerbations. This may explain why in hospitalized patients with concomitant COPD, compared to those without COPD, ACEi were less frequently applied [23].

## Potential Interactions Between COPD Medication and Heart Disease

Long-acting muscarinic antagonists (LAMA) have been one of the most important therapy options for COPD since the first drug of this class was approved in 2008. Since then, four substances—tiotropium, glycopyrronium, aclidinium bromide and umeclidinium—have been approved for inhaled use in COPD. Before 2008, only ipratropium, a short-acting muscarinic antagonist (SAMA), was available for inhaled use. A meta-analysis suggested significant adverse cardiovascular outcomes for studies comparing ipratropium with placebo and for all studies where either ipratropium of tiotropium was compared with placebo [24]. However, a randomized controlled study with tiotropium, delivered by the HandiHaler device, showed significant beneficial effects of tiotropium on adverse cardiac events [25]. After introduction of the Respimat inhaler for tiotropium, there were again safety concerns because of reports of adverse cardiovascular outcomes as compared with the tiotropium HandiHaler. However, a large prospective randomized controlled study with the Respimat device showed no evidence for increased cardiovascular adverse effects [26]. In conclusion, LAMA are considered safe in cardiac patients, although high-quality evidence for safety from large databases is only available for tiotropium.

**There is an excellent rationale for treating patients suffering from heart failure and COPD with both a beta$_1$ selective beta-blocker and an inhaled long-acting or ultra-long-acting beta$_2$ agonist.**

Theophylline (dimethylxanthine) has been used for airway obstruction since 1922. Xanthines are known to inhibit several phosphodiesterases (PDE-3, 4, 5, 7, 9) that are present in bronchial smooth muscle cells and inflammatory cells. This has bronchodilatory and anti-inflammatory effects [27]. However, xanthines also inhibit adenosine receptors (AR-A1, A2A, A2B, A3), which may cause cardiac side effects. Among the different xanthine drugs, doxophylline has strong PDE inhibitory effects and modest adenosine receptor effects, which translates into clinical superiority over other xanthines [28]. According to current guidelines, xanthines are not considered as first-line medications for COPD or asthma. However, in patients who do not tolerate beta agonists, they may still have a place, particularly in younger adults with no cardiac disease. A newly developed PDE inhibitor (roflumilast) is recommended for patients with severe COPD with productive cough who are not underweight [13]. The drug often causes diarrhea, nausea, and weight loss. This profile might be particularly advantageous to patients at risk for chronic heart disease due to over-nutrition.

Oral corticosteroids (OCS) should be avoided in the chronic treatment of COPD and asthma; however, some patients respond with frequent exacerbations after cessation of OCS. Interleukin-5 inhibitors have been approved to avoid or reduce OCS but only in asthma and not in COPD. During acute exacerbations of COPD and asthma, OCS with 0.5 mg/kg prednisolone for 5 days [29] is recommended because this therapy leads to relief of obstruction and symptoms and shortens the hospitalization [11]. Unfortunately, OCS are associated with a multitude of adverse events among which venous thromboembolism is of special interest for COPD patients because it may mimic COPD exacerbation [30] and is more difficult to diagnose than in patients

without structural lung disease. It is also of interest for chronic heart failure because these patients per se have a significantly increased risk for venous thromboembolism.

## Chronic Cor Pulmonale

Pulmonary disease may affect the heart, and the most obvious consequence of chronic lung disease on the heart is chronic cor pulmonale. This observation was made by ancient pathologists and defined as the presence of a dilated right ventricle in a patient without obvious left heart disease. However, the MESA COPD study, by means of systematic magnetic resonance imaging (MRI) and pulmonary function test (PFT), found that the right ventricular volume in stable COPD patients was smaller by about 8 ml compared with healthy matched controls [31]. There was a highly significant correlation between the degree of airway obstruction and the reduction of the right ventricular volume, and there was a highly significant correlation between the amount of emphysema and the reduction in right ventricular volume. This led to the hypothesis that the positive intrathoracic pressure in obstructive lung disease prevents blood flow into the thorax and causes underfilling of the heart.

A recent interventional study demonstrated that this hypothesis was true and that the mechanism was reversible. By means of a potent antiobstructive therapy, using an inhaled LABA/LAMA combination for 2 weeks in patients with severe COPD with no cardiac disease, the right ventricular volume increased by about 7 ml, along with a significant increase in stroke volume and cardiac output [32]. These changes were due to a significant reduction in the pulmonary residual volume and altogether resulted in a highly significant beneficial effect on dyspnea and quality of life. This suggests that air trapping, due to obstructive lung disease causes intrathoracic pressure increase, resulting in cardiac underfilling and hemodynamic stress and that these pathologic findings can be reversed by potent bronchodilatory therapy. However, such effects may be much less impressive if the patients suffer from some degree of left heart disease [33].

## Conclusion

In conclusion, the combination of chronic heart and lung diseases is very common in the elderly population. Patients should be treated for both diseases. Beta-blockers are very important drugs because their use is associated with significantly improved morbidity and mortality, and their combination with inhaled long-acting sympathomimetics makes sense from a pharmacological and a clinical point of view. There are numerous potential effects of heart medications on the diseased lung and of lung medications on the diseased heart. However, in most instances, such medication is justified, just as in cases where the other disease is not present.

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**Compliance with Ethical Guidelines**

**Conflict of Interest:** H. Olschewski, M. Canepa, and G. Kovacs declare that they have no competing interests.

For this article no studies with human participants or animals were performed by any of the authors. All studies performed were in accordance with the ethical standards indicated in each case.

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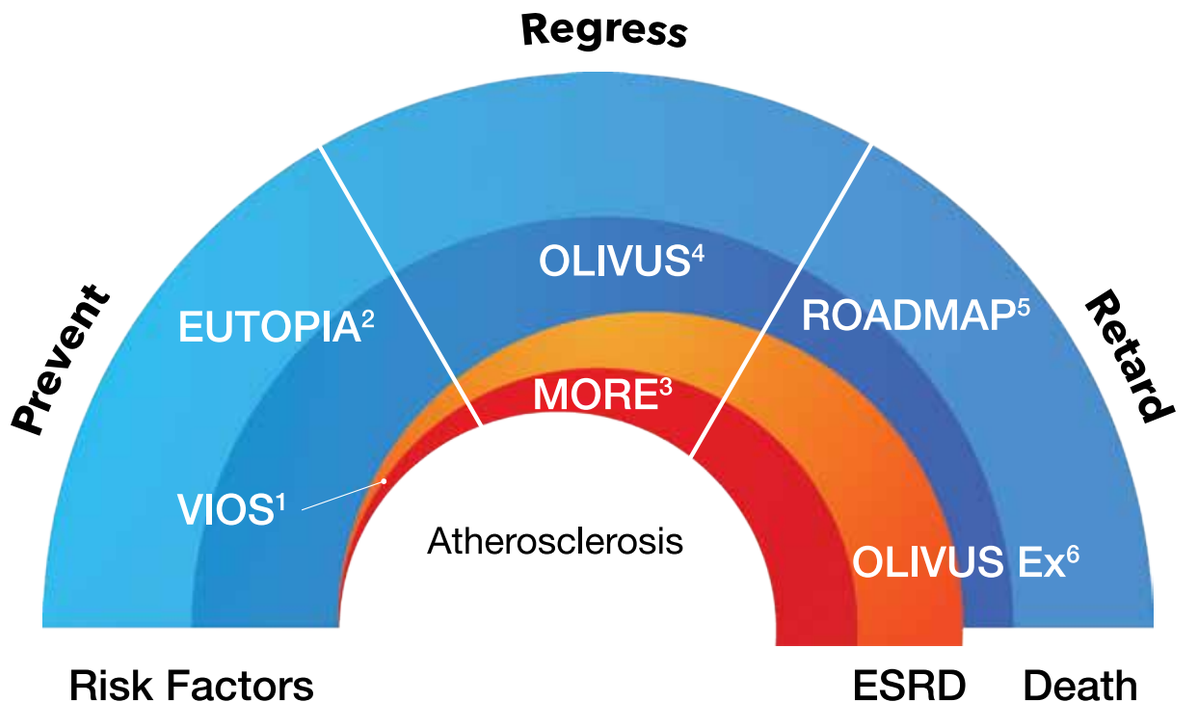


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