Narrative review

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Hypertension and stable coronary artery disease: an overview

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Systemic hypertension is highly prevalent in stable coronary artery disease, a pervasive comorbidity complicating the diagnostic performance and interpretation of non-invasive provocative tests in chest pain patients because of the ischaemic signals generated, despite normal or near normal coronary arteries, by hearts structurally readapted by long-term exposure to raised systemic blood pressure. Additional and unresolved problems posed by arterial hypertension in patients with stable coronary artery disease regard the benefits of antihypertensive treatment due to reports of irrelevant, if not detrimental, effect of blood pressure (BP) lowering in averting coronary relapses as well as the lack of association between BP levels and incident coronary events in survivors from acute myocardial infarction. Uncertainties extend to BP-independent cardioprotective effects of antihypertensive drugs, although the efficacy of renin–angiotensin system blockers in the long-term prevention of cardiovascular events in stable coronary artery disease patients has been shown by several studies, particularly when combined with amlodipine, a dihydropiridine calcium channel blocker. In contrast, the long-term effect of beta-blockers, the antihypertensive class most used in that clinical category, is not supported by strong evidence except that generated in patients with systolic dysfunction and early postmyocardial infarction recovery periods.

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Introduction

Despite the almost universal recognition of its importance as a coronary risk factor in healthy populations,[1] several aspects of the impact of arterial hypertension [blood pressure (BP) levels above a predefined cutoff, usually 140/90 mmHg, or ongoing antihypertensive treatment] in patients with established coronary artery disease (CAD) do not easily fit a simple cause–effect model. Problematic aspects regard the immediate and early phases of acute myocardial infarction (AMI) (see ref.[2] for a review) and extend to stable CAD, a heterogeneous, not mutually exclusive, clinical cluster including remote acute coronary syndromes, prior percutaneous transluminal coronary angioplasty or coronary artery bypass graft surgery, angiographically documented coronary stenosis and stable angina. In all those conditions, arterial hypertension affects about two-thirds of patients,[3,4] a pervasive comorbidity that mandates specific competence in hypertension management as well as thoughtful awareness of the underlying epidemiological and pathophysiological interconnections. The concept is highlighted further by the high rates of hypertension in the landmark randomized clinical trials (RCT),[5–14] some of which are listed in Table 1, which dictated the evolution of treatment strategies in the field.

On those premises, the present work will overview critically some implications of arterial hypertension in patients with stable CAD, a definition, this latter, deliberately preferred to ischaemic heart disease that, rather than a synonymous term, denotes more properly a multifactorial and complex pathophysiological process of which coronary atherosclerosis is only one component.[15] CAD, instead, in referring to anatomic coronary status, adapts better to the following discussion focused on diagnostic studies *ex post* validated by coronary angiography[16–28] as well as RCTs performed in patients carefully selected on the basis of obstructed epicardial coronaries[5–14] rather than ischaemic heart disease as defined above.[15]

The non-invasive diagnosis of coronary artery disease in hypertensive patients with chest pain

Chest pain, either the typical retrosternal discomfort triggered by physical exertion or emotional stress and

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Table 1 Prevalence of history of hypertension (HT), acute myocardial infarction (AMI), percutaneous transluminal coronary angioplasty (PTCA), coronary artery bypass graft surgery (CABG), treatment with beta-blockers (BB), calcium channel blockers (CCB), angiotensin-converting enzyme inhibitors (ACEI) or angiotensin II receptor blockers (ARB) in randomized clinical trials in stable coronary artery disease published from 2000 onward listed by publication year

Study[Ref]	*N*	HT%	AMI%	Angina%	PTCA%	CABG%	BB%	CCB%	ACEI/ARB%
HOPE[5]	9297	47	53	55	26	18	40	47	RAM
EUROPA[6,a]	12 218	25[b]	65	NR	29	29	63	32	PER
INVEST[7]	22 576	100	32	67	15	16	ATEN	VER	TRAN
CAMELOT[8]	1992	60	38	9[d]	28	8	76	AMLO	ENAL
PEACE[9]	8290	46	55	70	41	39	60	36	TRAN
ACTION[10]	7865	51	50	93	20[c]	See[c]	80	NIF	22
COURAGE[11]	2287	67	38	85	38	15	89	40	59
BEAUTIFUL[12,b]	10 917	72	89	NR	51[c]	See[c]	87	NR	90
ONTARGET[13]	25 620	69	49	35	29	21	57	33	TEL
TRANSCEND[14]	5926	76	46	48	26	19	58	40	TEL

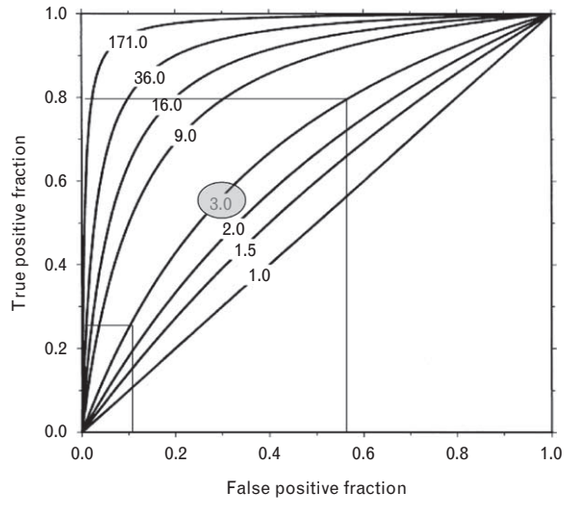
AMLO, amlodipine; ATEN, atenolol RAM, ENAL, enalapril; NIF, nifedipine; PER, perindopril; RAM, ramipril; TEL, telmisartan; TRAN, trandolapril; VER, verapamil refer to trial drugs. ACTION[10], A Coronary disease Trial Investigating Outcome with Nifedipine; BEAUTIFUL[12], morBidity-mortality EvAlUaTion of the If inhibitor ivabradine in patients with coronary disease and left-ventricULar dysfunction; CAMELOT[8], Comparison of Amlodipine vs. Enalapril to Limit Occurrences of Thrombosis; COURAGE[11], Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation; EUROPA[6], EURopean trial On reduction of cardiac events with Perindopril in stable coronary Artery disease; HOPE[5], Heart Outcomes Prevention Evaluation; INVEST[7], International Verapamil-Trandolapril Study; ONTARGET[13], ONgoing Telmisartan Alone and in combination with Ramipril Global EndpoinT; PEACE[9], Prevention of Events with Angiotensin Converting Enzyme Inhibition; TRANSCEND[14], The Telmisartan Randomised AssessmeNt Study in ACE iNtolerant subjects with cardiovascular Disease. [a] BP > 160/90 mmHg or ongoing antihypertensive treatment. [b] Stable CAD &EF < 40%. [c] Relative percentages of PCI vs. CABG not reported. [d] Canadian Cardiovascular Society class 4 (angina at any level of physical exertion).

relieved by rest or nitroglycerin, or atypical in its presentation, is an alarming symptom whose management hinges around the documentation of inducible ischaemia,[29] a temporally ordered sequence of regional perfusion defects, mechanical abnormalities and electrical disturbances, respectively. That so-called 'ischaemic cascade'[30] may be triggered in myocardial regions perfused by stenosed coronaries stressed by exercise or pharmacological agents such as dobutamine (DOB), an alpha-1 and beta-agonist, or dipyridamole (DIP), an adenosine breakdown inhibitor. As a result of those hyperaemic stimuli, blood flow diverts from ischaemic to non-ischaemic territories and from subendo to subepicardial areas and the ensuing flow heterogeneity, which constitutes the pathophysiological background of inducible ischaemia,[30] evokes the diagnostic array of scintigraphic, echocardiographic and electrocardiographic changes familiar to all cardiologists. Not dissimilar ischaemic signals, however, are generated in hypertensive hearts readapted by long-term exposure to raised systemic BP,[31,32] thus complicating the interpretation of non-invasive provocative tests used to diagnose flow-limiting coronary stenoses.[33] In that context, the diagnostic performance of non-invasive provocative tests for the identification of flow-limiting coronary stenoses differs markedly, a behaviour better understood by some preliminary explanation of the operating characteristics of diagnostic tests.

The operating characteristics of diagnostic tests

A binary (either positive or negative; dubious results need retesting) screening test aims both to maximize the identification of positives (the so-called true positive fraction, TPF, also known as sensitivity) and minimize misclassification of negatives (the so-called false-positive fraction, FPF, also known as 1-specificity), the two parameters plotted in receiver operating characteristic (ROC) curves (Fig. 1). Perhaps less known is that TPF and FPF are univocally defined by their odds ratio (OR, derived from the following relationship: $[TPF/(1-TPF)] \times [(1-FPF)/FPF]$), a general index of the strength of a relationship between binary data, be it a diagnostic outcome (positive/negative), a risk factor (present/absent) or a disease status (disease/no disease).[34]

Fig. 1



Correspondence between true-positive (i.e. sensitivity) and false-positive (1-specificity) fraction of a binary diagnostic test and diagnostic odds ratios (ORs). Diagnostic ORs differ quite markedly from those used in epidemiological or intervention studies: for example, an OR of 3 (shaded area), a highly satisfactory outcome in those latter contexts, profiles a poor diagnostic test that either mislabels about 60% of controls at TPF = 0.80 or identifies only 25% or so of cases at FPF = 0.10. Modified from[34].

Quite importantly, the ORs required for reasonable diagnostic accuracy are far larger than those needed to hypothesize relevant cause–effect relationships in epidemiological or intervention studies (Fig. 1). Thus, only unusually strong, independent risk factors can markedly improve the distinction of healthy from diseased individuals, an important concept explaining why 'emerging' risk factors not provided of such strength, after initial enthusiasm, are bound to be abandoned in daily clinical practice.[35]

Positive predictive power (PPV, the ratio of true-positive results to both true-positive and false-positive results), that is the probability that a person with a positive test has coronary stenosis at coronary angiography, is a next qualifier of a diagnostic test heavily conditioned by disease prevalence according to the Bayes' theorem of conditional probability. Thus, PPV of a positive echo DOB (assuming, as an example, the summary value of TPF = 0.88 and FPF = 0.13 reported in Table 2), administered in 1000 individuals, would average 36% if disease prevalence is 5%, [44/(44 + 124)], in, say, a younger, non-smoking hypertensive woman with atypical chest pain, rising to 87%, [440/(440 + 65)], that is close to certainty, for disease prevalence of 50% as in a middle-aged hypertensive, dyslipidaemic male smoker with typical chest pain, showing quite clearly the essential contribution of clinical judgement to diagnostic work-up.

In contrast to PPV, negative predictive value (NPV) (the ratio of true-negative results to both true-negative and false-negative results), that is the probability that a person with a negative (N) test does not have a disease as assessed by a golden standard, would be unchanged in both conditions [88%; (827/(827 + 123) and 435/(435 + 60), respectively] so that, independent of disease prevalence and specificity, a negative outcome obtained by a highly sensitive test would practically exclude significant obstructive epicardial coronary disease.

The diagnostic performance of non-invasive stress tests in hypertensive patients with chest pain

Table 2 provides the diagnostic ORs and other indicators of diagnostic performance of non-invasive stress tests for the detection of coronary stenoses in hypertensive patients with chest pain. The table compiles a series of angiographically validated studies comparing electrocardiogram (EKG) exercise stress, stress echocardiography and SPECT[16–28] and does not refer to diagnostic techniques still sparsely validated in hypertensive patients, such as exercise echocardiography, nuclear computed tomography, MRI and PET reviewed in previous work, which the interested reader is referred to.[33]

The unsatisfactory specificity of EKG exercise stress test as a screening test for CAD in hypertensive patients with

Table 2 Performance of diagnostic stress tests for detection of flow-limiting coronary stenoses in hypertensive patients with chest pain as verified by ex-post coronary angiography

Test	OR	*N*	CAD *N* (%)	TPF (%)	FPF (%)	PPV (%)	NPV (%)	Author[Ref]
EKG exercise stress	1.1	43	21 (49)	0.72	0.71	49	52	Senior *et al.*[16]
	1.4	137	101 (74)	0.58	0.49	77	30	Elhendy *et al.*[17]
	1.5	43	29 (67)	0.67	0.58	71	38	Picano *et al.*[18]
	4.4	197	116 (59)	0.77	0.43	72	63	Pasierski *et al.*[19]
	4.5	35	17 (49)	0.82	0.50	61	75	Cortigiani *et al.*[20]
	4.9	59	22 (37)	0.68	0.30	57	79	Maltagliati *et al.*[21]
	5.4	76	24 (31)	0.81	0.44	46	86	Lu *et al.*[22]
Median	**4.4**	**590**	**330 (56)**	**0.72**	**0.50**	**61**	**63**	
echo DIP	15.8	101	57 (56)	0.61	0.09	90	64	Fragasso *et al.*[23]
	15.8	76	24 (31)	0.61	0.09	76	83	Lu *et al.*[22]
	23.3	43	29 (67)	0.67	0.08	95	57	Picano *et al.*[18]
	36.8	35	17 (49)	0.82	0.11	88	84	Cortigiani *et al.*[20]
	171.0[a]	53	23 (43)	0.78	0	100	86	Astarita *et al.*[24]
Median	**23.3**	**308**	**150 (49)**	**0.73**	**0.09**	**90**	**84**	
echo DOB	13.2	84	66 (79)	0.73	0.17	94	46	Elhendy *et al.*[25]
	23.4	101	57 (56)	0.88	0.20	85	84	Fragasso *et al.*[23]
	35.9	30	18 (60)	0.93	0.27	84	87	Ariff *et al.*[26]
	76.9	76	24 (31)	0.87	0.08	83	94	Lu *et al.*[22]
	147.4	197	116 (59)	0.75	0.02	98	73	Pasierski *et al.*[19]
	171.0[a]	43	29 (67)	0.93	0	100	87	Senior *et al.*[16]
Median	**56.4**	**531**	**310 (59.5)**	**0.88**	**0.13**	**90**	**86**	
SPECT	7.7	137	101 (74)	0.75	0.28	88	51	Elhendy *et al.*[17]
	9.9	84	66 (79)	0.67	0.17	94	41	Elhendy *et al.*[25]
	10.1	76	24 (31)	0.90	0.47	47	92	Lu *et al.*[22]
	27.6	101	57 (56)	0.98	0.64	67	94	Fragasso *et al.*[23]
	27.8	92	18 (20)	0.94	0.36	39	98	Prisant *et al.*[27]
	62.7	50	32 (64)	0.80	0.06	96	73	Aggeli *et al.*[28]
	87.3	53	23 (43)	1.0	0.53	59	100	Astarita *et al.*[24]
Median	**27.6**	**593**	**340 (54)**	**0.90**	**0.36**	**67**	**92**	

Data on electrocardiogram (EKG) exercise stress test refer to studies in which the procedure has been used for paired comparison with other stress tests. CAD, coronary artery disease prevalence; echo DIP, dipyridamole stress echocardiography; echo DOB, dobutamine stress echocardiography; FPF, false-positive fraction; NPV, negative predictive value; OR, odds ratio; PPP, positive predictive values; SPECT, single-photon emission computed tomography; TPF, true-positive fraction. [a] Approximated to the maximum.

chest pain emerges quite clearly from diagnostic ORs which are six to 10-fold lower than the other provocative techniques. More specifically, the median FPF value of 0.50 reported in Table 2 implies that reliance upon EKG exercise stress test would expose half of positives to useless, costly and potentially risky medical procedures. On the contrary, the median TPF of 0.72 means that one-third or so of haemodynamically significant coronary stenoses would not be detected, a poor result notably obtained despite the high CAD prevalence (Table 2) that, according to Bayes's postulates, optimizes diagnostic performance. Thus, EKG exercise stress test is neither specific enough to identify reliably CAD when positive, nor as sensitive as to exclude confidently its presence when negative, an important limitation bailed out by its potential in assessing exercise tolerance, chronotropic and BP response, and long-term risk stratification.

Different conclusions are provided by DIP and DOB stress echography whose specificity in hypertensive patients is high enough to virtually exclude flow-limiting coronary stenosis in case of negative results, albeit sensitivity of the two tests differs in favour of DOB, an advantage counterbalanced by more frequent serious side effects[36] so that the choice between them should better be left to the expertise developed at each single centre. Table 2 also shows the performance of myocardial perfusion imaging that, despite its elevated sensitivity in the detection of flow-limiting coronary stenoses in hypertensive patients, is about four-fold less specific than stress echography, a disadvantage amplified by the environmental and long-term concerns related to the use of radioactive tracers for myocardial imaging.[37]

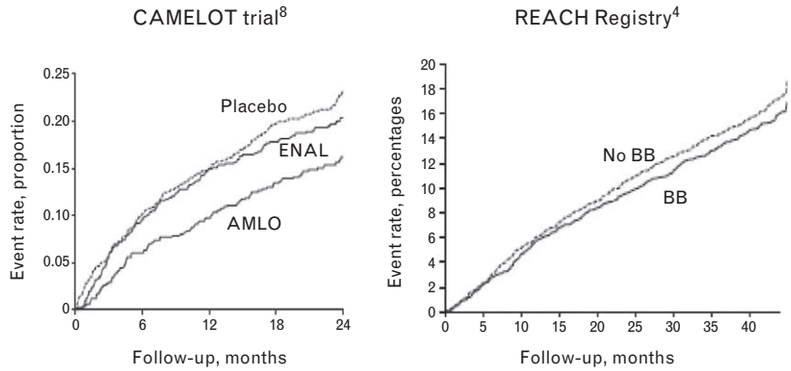
Beyond their specific metrics, however, it should be kept in mind that diagnostic performance is strongly affected by selection (only more 'worrying' chest pain patients tend to be referred for non-invasive and angiographic screening) and verification (angiographic verification of stenosis tends to be reserved to test-positives and withheld in test-negatives) biases.[38] Both attitudes likely contributed to the unsatisfactory performance of provocative tests for inducible ischaemia reported in a largely hypertensive group of patients referred to angiography in whom, quite disturbingly, preangiographic testing did not raise the discriminatory power above that obtained by clinical evaluation.[39] On the contrary, adoption of coronary angiography as a verification standard for ischaemic heart disease clearly led to labelling as false positives a large portion of high-risk angina patients, women more frequently,[40] with ischaemic heart disease despite a patent epicardial coronary tree.[15]

As a second consideration, stress tests have frequently been applied to screen silent ischaemia in asymptomatic hypertensive individuals with unfavourable risk profiles but no prior history of ischaemic heart disease,[41] an approach based upon the background assumption that unveiling and subsequent repair of advanced CAD at a preclinical stage may prevent cardiac outcomes. However, that strategy is burdened, if applied on a large-scale basis, by intolerable costs, considerable risks and being unlikely to guarantee a consistent return at least as compared with the benefits afforded by effective pharmacological treatments and lifestyle changes, for example.[42] Although early identification of inducible ischaemia may help to improve risk stratification,[43] screening tests should, however, do more than that,[44] at least prompt providers to increase use of evidence-based medical therapies and patients to comply with their prescriptions, two expectations unmet in a high-risk hypertension-prone condition such as asymptomatic type 2 diabetes.[45] As a result, diabetological guidelines now discourage screening in asymptomatic diabetic patients,[46] although cardiological guidelines leave that option open in high-risk individuals, but recommendations in the field are highly inconsistent, with only a minority specifically factoring cost into their algorithms.[47]

The management of hypertension in patients with stable coronary artery disease

Although the benefits of antihypertensive treatment are incontrovertible, it must be recognized that most of the available evidence derives mainly from studies in uncomplicated hypertensive patients[48] extended by inference to stable CAD. As a matter of fact, studies in that specific setting specifically directed to evaluate BP lowering vs. placebo are missing and the only trial targeting that category compared two different treatment regimens[7] and RCTs with angiotensin-converting enzyme inhibitors (ACEIs),[5,6,8,9] angiotensin II type 1 receptor blockers (ARBs)[13,14] and calcium channel blockers (CCBs)[8,10] were, rather paradoxically, carried out to test BP-independent properties in mixed normotensive and hypertensive cohorts. Thus, the positive long-term results first reported with an ACEI such as ramipril in the HOPE study,[5] confirmed by some[6] but not other studies[8,9] using different congeners, opened the way to the use of ACEIs and possibly ARBs[13,14] in stable CAD,[49] an indication *a fortiori* stronger in the presence of comorbid hypertension.[49] With regard to CCBs, nifedipine, a dihydropiridine (DHP) derivative and an effective antihypertensive drug,[48] was evaluated in patients with stable angina pectoris[10] in a trial that, while settling concerns about its long-term safety in CAD patients,[50] provided no evidence of long-term protection from hard events.[10] Similarly, verapamil, a phenylalkylamine CCB derivative, combined with trandolapril, an ACEI, did not differ from an atenolol along with hydrochlorothiazide-based regimen in hypertensive patients with stable CAD.[7] Different from both drugs, amlodipine, a DHP with potent antianginal properties[51] and well tolerated in severe congestive heart failure,[52] decreased cardiovascular events as compared with both placebo and enalapril, an ACEI[8] (Fig. 2, left panel). Moreover, amlodipine in

Fig. 2

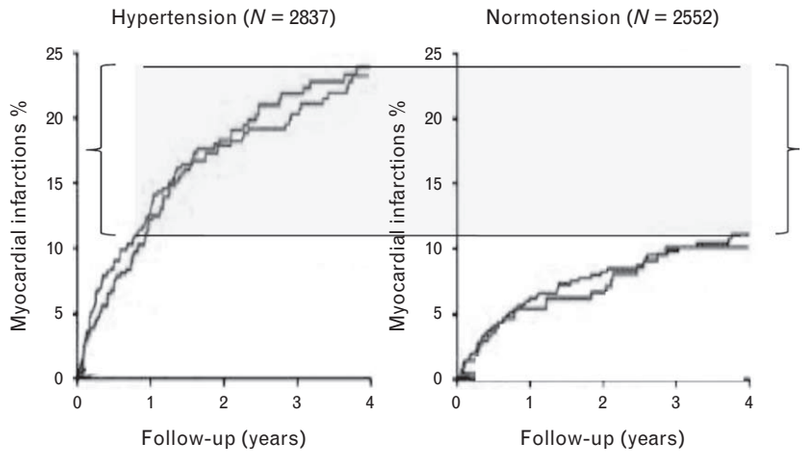


Left panel: Reduced cardiovascular event rate (cardiovascular death, non-fatal AMI, resuscitated cardiac arrest, coronary revascularization, hospitalization for angina pectoris, hospitalization for congestive heart failure, fatal or non-fatal stroke or transient ischaemic attack, and peripheral vascular disease) in stable CAD patients on amlodipine (AMLO) as opposed to the neutral effect of enalapril (ENAL), an ACEI. Right panel: No difference in cardiovascular events (cardiovascular death, non-fatal MI or non-fatal stroke) in stable CAD patients on long-term beta-blockers (BB) or not. Modified from[8] and [4], respectively. ACEI, angiotensin-converting enzyme inhibitor; AMI, acute myocardial infarction; CAD, coronary artery disease; MI, myocardial infarction.

combination with different ACEIs[53,54] prevented cardiovascular events more effectively than a more conventional diuretic along with ACEI[53] or atenolol[54]-based regimen in high-risk hypertensive patients, an outcome, to some extent, consistent with posthoc analyses of the EUROPA study.[55] Thus, the association of amlodipine with renin–angiotensin system inhibitors applies to first choice treatment in stable CAD, a still inferential hypothesis whose background evidence, though, is stronger than that available for beta-blockers, the pharmacological class by far most prescribed in stable CAD patients (Table 1). Apart from systolic heart failure[56] and early post-AMI recovery periods,[57] in fact, the evidence in support of the long-term use of beta-blockers is negative[58] and their efficacy has been questioned even in uncomplicated hypertension.[59] Most recently, data from the REACH study showed no difference between CAD patients on beta-blockers and not (Fig. 2, right panel), a result highly pertinent to the present context, as patients included in that registry are hypertensive by 80%.[4]

A related but distinct problem raised by the coexistence of arterial hypertension in stable CAD considers the appropriateness to maintain BP at levels lower than the 140/90 mmHg cutoff conventionally accepted in

Fig. 3



Incidence of acute myocardial infarctions by blood pressure status in coronary artery disease patients with inducible ischaemia at stress echo. Shaded area between graphs quantifies the impact added by a hypertensive background independent of the presence (dark lines) or absence (lighter lines) of resting wall motion abnormalities. Modified from[68].

the uncomplicated hypertensive population.[48] Such a proposal, put forward only few years ago,[60] equalized stable CAD to diabetes and chronic renal failure for which, at that time, BP values below 130/80 mmHg or less were recommended to achieve protection from cardiovascular events.[48] However, a reappraisal of all trials of antihypertensive agents in patients with CAD found no scientific ground for those recommendations,[61] nowadays under revision even with regard to diabetes[62] and chronic renal failure.[63] Achievements of more stringent BP targets in stable CAD also conflict with the poor BP control characterizing daily clinical practice,[64] lack of association between BP levels with relapsing coronary events in long-term follow-ups of post-AMI patients[65] and recurring reports of the neutral,[66] if not detrimental,[67] effect of BP lowering on acute coronary events compensated, to some extent, by a reduced stroke incidence.[2] On the contrary, it must be considered that raised systemic BP values are merely one of the several and interacting proatherogenic components of the hypertensive syndrome.[1] Moreover, a hypertensive background unequivocally compounds the negative prognostic impact carried by inducible ischaemia *per se*[68] (Fig. 3), although the reasons for that noxious interaction are not clearcut. Hypertension-related, more serious and/or faster progressing atherosclerotic CAD may perhaps contribute to that evolution, but, even were that the case, repair of the diseased coronary segments does not seem to provide the definitive therapeutic answer. In fact, coronary revascularization in individuals with severe CAD has provided uncertain results,[69] apparently independent of coexisting inducible ischaemia.[70] Transluminal coronary angioplasty, on the contrary, applied in patients with less advanced CAD does not decrease death, myocardial infarction rates or the need for subsequent revascularization[71] as compared with optimal medical therapy,[11] a conclusion reminiscent of the outcome of renal angioplasty in the cognate field of atherosclerotic renovascular disease.[72]

In conclusion, stress echocardiography provides a highly sensitive and specific tool for the non-invasive identification of haemodynamically significant coronary stenosis in the hypertensive patient with chest pain in whom the readaptation process in response to long-term exposure to raised BP confounds the diagnostic process. However, unanswered questions await responses such as, for example, whether BP lowering benefits or not hypertensive patients with stable CAD. Uncertainties extend to cardioprotective effects of antihypertensive drugs, although renin-angiotensin system blockers, particularly when combined with amlodipine, a DHP calcium channel blocker, are promising in that regard. On the contrary, no evidence supports at the moment the long-term use of beta-blockers in that specific clinical category while reopening of stenosed coronaries *per se* does not protect from ischaemic relapses.

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