

ORIGINAL ARTICLE

Evaluation of the efficacy and tolerability of the combination delapril plus indapamide in the treatment of mild to moderate essential hypertension: a randomised, multicentre, controlled study

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The aim of the study was to evaluate efficacy and tolerability of two different fixed combinations of an angiotensin-converting enzyme inhibitor and a diuretic: delapril+indapamide (D+I) and captopril+hydrochlorothiazide (C+H) administered for 6 months to patients with mild to moderate essential hypertension. In all, 96 centres participated in this randomised, parallel groups, controlled study. A total of 829 patients with uncomplicated mild to moderate hypertension were randomised, and 790 were eligible for the analysis of efficacy (intention to treat). Patients of both sexes, aged 18–75 years, newly diagnosed or untreated during the last month were included in the study if their diastolic blood pressure (DBP) was ≥ 95 and ≤ 114 mmHg. The starting doses of the drugs were delapril 30 mg+indapamide 1.25 mg tablets o.d. or captopril 50 mg+hydrochlorothiazide 15 mg tablets o.d. After a 1-month treatment period, nonresponders (DBP > 90 mmHg, or decrease in DBP < 10 mmHg) had the daily dose increased to either delapril 30 mg+indapamide 2.5 mg or captopril 50 mg+hydrochlorothiazide 25 mg tablets for a further 5 months. The primary assessment of antihypertensive

efficacy was the percentage of patients who responded after a 6-month drug treatment. The responder rates were 72.6% with D+I and 62.9% with C+H ($P=0.004$ between treatments) after 60 days of treatment, and 92.6% in the D+I and 85.2% in the C+H ($P<0.001$ between treatments) at the end of the treatment period. The final value of systolic blood pressure was 134.5 ± 13.1 mmHg with D+I and 138.3 ± 14.0 mmHg with C+H ($P<0.001$ between treatments). At the final visit, DBP was 84.5 ± 7.0 mmHg in the D+I group and 85.5 ± 8.0 mmHg in the control group ($P=0.017$ between treatments). In all, 11 patients in the D+I group and 19 patients in the C+H group were withdrawn from the study because of adverse events. In all, 30 patients (7.6%) with D+I and 32 patients (8.1%) with C+H experienced adverse events. In conclusion, D+I was more effective than C+H in terms of overall reduction in blood pressure and response rate. Greater efficacy was obtained without any increase in adverse effects, since both treatments were equally well tolerated.

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Introduction

Essential hypertension is a chronic disease, which usually requires life-long treatment. One of the most important problems in the treatment of such a generally asymptomatic condition, such as arterial hypertension, is patient compliance. Tolerability is therefore an essential requisite for antihypertensive medication, since any alterations in patient

well-being may dramatically reduce adherence to therapy.

On the other hand, antihypertensive treatment should not only be well tolerated but also effective in terms of blood pressure reduction. However, low-dose monotherapy is usually able to normalise blood pressure in less than 40–50% of mild to moderate hypertensive patients.^{1,2} Recent studies have demonstrated that normalisation of blood pressure values during therapy may be obtained by two different strategies. The first one is to increase the dosage of the single drugs until the maximum tolerated dose is reached.³ In this case, satisfactory blood pressure reduction may sometimes be obtained at the expense of an increased incidence of

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adverse events. When monotherapy does not produce sufficient efficacy, combination therapy may help, since the combination of two drugs may not only determine an additive effect on blood pressure^{1,4,5} but may also be associated with a lower incidence of unwanted effects, as the dosage of both drugs may be reduced.⁶ This second strategy may therefore be better tolerated, but an additional problem is the increase in the number of daily tablets that have to be taken, with consequent reduction in patient compliance. However, fixed combination therapy offers the advantage of once-daily administration together with the effectiveness of the combination of two drugs at convenient dosages.

In this regard, the combination of an angiotensin-converting enzyme (ACE) inhibitor with a diuretic has proven to be particularly advantageous for pharmacokinetic and pharmacodynamic reasons.⁷⁻⁹ The addition of an ACE inhibitor may blunt a possible reduction in serum potassium induced by the diuretic, while the inhibition of the renin-angiotensin-aldosterone system may be particularly effective when it is activated by the diuretic-induced water depletion.⁴

Some of the combinations may be more effective than others. In particular, the combination of delapril with indapamide may be particularly useful.¹⁰⁻¹⁴

Indapamide is a nonthiazide chlorosulphonamide derivative of indole, which has been known to have long-acting hypotensive effects,¹⁵ with minimal diuretic activity at least at the recommended dosage of 2.5 mg/daily.¹⁶ It is a lipophilic substance that is rapidly absorbed from the gastrointestinal tract, and has a biological half-life of about 18 h, which allows once-daily dosing. Indapamide preferentially binds to vascular smooth muscle cells, inducing relaxation and, consequently, vasodilatation.¹⁷

Delapril is a nonsulphydryl ACE inhibitor with high specificity for the C-terminal of the peptide located in vessels and myocardium.¹⁸ Delapril is an esterified prodrug that is converted, *in vivo*, into active metabolites.¹⁹ It is rapidly absorbed after oral administration: the active metabolites (M-I and M-III) may be detected in serum and urine.

The efficacy and safety of delapril and indapamide were assessed in experimental studies in which the combination of the two drugs was compared with the single substances,^{20,21} but no large comparative study is available vs other fixed combinations.¹⁴

Therefore, the aim of our study was to compare the efficacy and the tolerability of the combination D+I with a control group treated with the combination C+H in more than 800 patients with mild to moderate hypertension.

Patients and methods

This multicentre, randomised, parallel groups controlled study was conducted in accordance with the

guidelines of good clinical practice: prior to the beginning of the study, the protocol was approved by the Ethics Committee, and informed consent was obtained from all patients. In all, 96 centres participated in the study.

Patients

Patients with diagnosis of mild to moderate essential hypertension, sitting diastolic blood pressure (DBP) between 95 and 114 mmHg at the end of a 4-week run-in period and aged between 18 and 75 years, were eligible for the study. Patients with secondary forms of hypertension or with any disease that could have interfered with the study protocol were excluded.

In particular, patients meeting at least one of the following criteria were excluded: borderline hypertension, DBP ≤ 94 or > 114 mmHg; systolic blood pressure (SBP) > 220 mmHg, grade III or IV hypertensive retinopathy, orthostatic hypotension (fall in blood pressure of at least 30 mmHg after 1 min of orthostatism vs the supine value, with symptoms such as dizziness, etc), any serious systemic disease (ie liver diseases, renal diseases, etc), diseases that can develop into any form of secondary hypertension (ie hyperthyroidism, pheochromocytoma, etc), systemic collagen disorders, insulin-dependent diabetes mellitus, neutropenia (white blood cells < 3500 /dl) and/or anaemia (red blood cells < 3500000 /dl or haemoglobin < 11 g/l), myocardial infarction and/or cerebrovascular accident within 6 months, congestive heart failure, cardiac valvular diseases clinically significant, chronic stable or unstable angina pectoris, aortic stenosis, atrial fibrillation and/or life-threatening arrhythmias, history of angioneurotic oedema, history of hypertensive encephalopathy, mental disorders, female patients of childbearing potential who, in the opinion of the investigator, were not taking adequate contraceptive measures, pregnancy or breast feeding, laboratory values clinically outside the normal range, known allergies to the study drugs, concomitant medication with other antihypertensive drugs, concomitant treatment with lithium, anti-MAO, other neuroleptics, indomethacin, steroids or potassium (both oral or parenteral administration) and antiacids.

Study protocol

Patients on antihypertensive treatment meeting the inclusion/exclusion criteria entered a 4-week pharmacological wash-out period. Thereafter, eligible *de novo* and previously treated patients were randomised, and entered the active phase of treatment. The observers were not blinded to which treatment the patients were going to have.

At the end of the wash-out period (baseline), the patients whose sitting peak DBP met the inclusion

criteria were included in the 6-month active treatment phase (efficacy phase), during which they were examined at 4-week intervals. The patients were randomised to either delapril 30 mg+indapamide 1.25 mg once daily (D+I) or captopril 50 mg+hydrochlorothiazide 15 mg once daily (C+H).

After 1 month of treatment, patients with sitting DBP ≤ 90 mmHg or in whom DBP fell from baseline by ≥ 10 mmHg were considered as 'responders'; otherwise patients were considered as 'nonresponders'. Nonresponder patients increased the dose of the diuretics (D+I: delapril 30 mg+indapamide 2.5 mg; C+H: captopril 50 mg+hydrochlorothiazide 25 mg), while responders were maintained on the same drug dosage until the end of the study. Nonresponder patients to the higher dose were definitely withdrawn from the study and allocated to a new antihypertensive treatment.

Measurements

Eligible patients were submitted to a thorough clinical examination, including electrocardiogram, chest X-ray and routine haematology and serum biochemistry tests.

SBP and DBP were evaluated during the morning in the sitting position, prior to drug intake (through effect), before wash-out, at baseline, and after 30, 60, 120 and 180 days of active treatment, using a mercury sphygmomanometer. The mean of three consecutive readings after a 5 min rest in the sitting position was considered. DBP was taken at Korotkoff phase IV, when disappearance of the sound (Korotkoff phase V) could not be identified. Adverse events were recorded by interviewing the patients.

Statistical analysis

The primary end point of the study was the percentage of responders during treatment. The

secondary end points were the reduction of DBP and SBP at each visit, reduction of pulse pressure (PP), patients normalised with DBP ≤ 85 mmHg, tolerability and safety of the two study treatments. At baseline, the medical history and demographic data between the two groups were compared by means of the χ^2 test or one-way analysis of variance (ANOVA). The effect of each treatment on blood pressure and heart rate was estimated at each visit calculating the 95% confidence interval of mean change vs basal value (visit 2, end of run-in period). DBP and SBP at the end of the efficacy phase were compared by means of an ANCOVA model, taking baseline values as covariate. The 'treatment by centre interaction' was included in the model. Comparison between treatments was also performed at each visit, on percentage of responders by means of χ^2 tests. The analysis was performed in the 'intention-to-treat' population (all patients randomised and with at least one control visit after baseline evaluation). A total sample size of 788 patients was calculated in order to have a 90% power to detect, with $\alpha = 5\%$ and a two-tailed test, a difference of 8% points, assuming an 82% success rate in C+H-treated patients. The safety evaluation included all the patients who took at least one dose of active treatment.

Results

Patients

Of the 829 patients screened for the study, 790 were randomly assigned to the two treatment groups: 396 to the D+I group and 394 to the C+H group. The two groups were comparable at baseline, and no difference in demographic and clinical variables was observed (Table 1). Data about previous antihypertensive treatment are reported in Table 2.

Table 1 Demographic and clinical data at entry (data expressed as mean \pm s.d.)

	Delapril+indapamide	Captopril+hydrochlorothiazide	P
Patients	396	394	
Males (%)	55.8%	52.3%	NS
Age (years)	54 \pm 11 (range 24–82)	54 \pm 11 (range 21–75)	NS
Weight (kg)	77 \pm 14	75 \pm 14	NS
Height (cm)	170 \pm 10	170 \pm 10	NS
Positive family history of hypertension	271 (69%)	286 (73%)	NS
No alcohol intake	216 (55%)	233 (60%)	NS
Smokers	95 (24%)	89 (23%)	NS
Retinopathy II stage KW	19 (6%)	21 (6%)	NS
Heart disease	40 (10%)	39 (10%)	NS
Kidney disease	17 (4%)	21 (5%)	NS
Other organ damages	12 (3%)	18 (5%)	NS
DBP (mmHg)	101.6 \pm 4.7	101 \pm 4.8	NS
SBP (mmHg)	160.6 \pm 14.3	160.1 \pm 14.2	NS
HR (beats/min)	74.5 \pm 9.4	73.9 \pm 8.8	NS

NS=no statistically significant difference between groups.

Table 2 Previous antihypertensive treatment

	<i>Delapril+indapamide</i>	<i>Captopril+hydrochlorothiazide</i>
Total number of patients	396	394
Patients with previous antihypertensive treatment	28 (7.0%)	24 (6.1%)
Number of patients previously treated with ACE inhibitors	13 (3.3%)	8 (2.0%)
Number of patients previously treated with diuretics	2 (0.5%)	2 (0.5%)
Total number of drugs		
1	17 (4.3%)	16 (4.1%)
2	11 (2.8%)	6 (1.5%)
3	0	2 (0.5%)

Table 3 Number and percentage of patients 'responders' to study treatment (intention-to-treat population)

	<i>Days of treatment</i>			
	<i>30 days</i>	<i>60 days</i>	<i>120 days</i>	<i>180 days</i>
<i>Delapril+indapamide</i>				
Responders	286 (72.6%)	355 (90.1%)	363 (92.1%)	365 (92.6%)
Non responders	108 (27.4%)	39 (9.9%)	31 (7.9%)	29 (7.4%)
<i>Captopril+hydrochlorothiazide</i>				
Responders	246 (62.9%)	326 (83.4%)	335 (85.7%)	333 (85.2%)
Non responders	145 (37.1%)	65 (16.6%)	56 (14.3%)	58 (14.8%)
<i>Comparison between groups</i>				
χ^2	8.407	7.724	8.296	11.12
<i>P</i> -value for χ^2	0.004	0.005	0.004	<0.001

'Responders'=patients with DBP \leq 90 mmHg or fall from baseline value \geq 10 mmHg.

Blood pressure and heart rate

After 30 days of treatment, the percentage of responders was 72.6% in the D+I group and 62.9% in the C+H group, this difference being statistically significant ($P=0.004$ χ^2 comparison between treatments). According to the protocol, the doses were increased in all the nonresponder patients. Therefore, 27.4% of the patients treated with D+I and 37.1% of those treated with C+H progressed to the higher dose of the drugs.

In total, 41 patients (10.3%) treated with D+I and 53 patients (13.4%) treated with C+H were withdrawn because of no response to the higher dose.

In the D+I group, the response rate increased to 90.1% at 60 days of treatment, to 92.1% at 120 days and to 92.6% at the final visit. At the same time interval, the response rate in the C+H group was 83.4, 85.7 and 85.2%, respectively. A statistically significant difference was present at each of the visits in favour of the D+I group (Table 3). Similar results were obtained when the percentage of patients with DBP \leq 90 mmHg (normalized patients, Table 4) and with \leq 85 mmHg was considered (62.4% in the D+I group and 56.5% in the C+H group, with a significant difference between treatment at 30, 60 and 120 days of treatment). At all time points, and especially at the end of the efficacy phase, peak SBP and DBP was significantly reduced

by both treatments (Table 5), but the extent of the reduction was greater with D+I (ANCOVA $P<0.001$ for SBP, $P<0.05$ for DBP). The mean reductions in DBP at the end of the treatment were 17.1 mmHg in the D+I group and 15.5 mmHg in the C+H group ($P=0.016$ ANCOVA between treatments). The SBP fell by 26.1 and 21.8 mmHg in the D+I and C+H groups, respectively ($P=0.041$ ANCOVA between treatments). The PP was significantly reduced by 9.0 and 6.3 mmHg in the D+I and C+H groups, respectively (ANCOVA $P<0.001$ between treatments). No significant change in heart rate (HR) was observed throughout the study with any treatment.

Safety result

After randomisation, 11 patients (2.7%) in the D+I group and 19 patients (4.7%) in the C+H group were withdrawn from the study because of adverse events. A total of 41 adverse events were recorded in 30 patients (7.6%) in the D+I treatment group and a total of 49 adverse events was recorded in 32 patients (8.1%) in the C+H group. A trend towards a higher percentage of moderate (48.4 vs 38.5%) and severe (6.5 vs 3.8%) adverse events was recorded in the C+H treatment group, compared with the D+I group. The most frequent adverse event was 'disorder of the respiratory system'. None of the adverse

Table 4 Number and percentage of patients 'normalized' to study treatment during the study (intention-to-treat population)

	Days of treatment			
	30 days	60 days	120 days	180 days
<i>Delapril+indapamide</i>				
Normalized	247 (62.7%)	321 (81.5%)	343 (87.1%)	343 (87.1%)
Not normalized	147 (37.3%)	73 (18.5%)	51 (12.9%)	51 (12.9%)
<i>Captopril+hydrochlorothiazide</i>				
Normalized	220 (56.3%)	295 (75.4%)	311 (79.5%)	312 (78.8%)
Not normalized	171 (43.7%)	96 (24.6%)	80 (20.5%)	79 (20.2%)
<i>Comparison between groups</i>				
χ^2	3.361	4.216	7.974	7.487
<i>P</i> -value for χ^2	0.067	0.040	0.005	0.006

'Normalized'=patients with DBP \leq 90 mmHg.

Table 5 SBP and DBP during the entire 6-months efficacy phase (intention-to-treat population)

	Days of treatment				
	Baseline	30 days	60 days	120 days	180 days
<i>SBP</i>					
<i>Delapril+indapamide</i>					
Mean \pm s.d. (mmHg)	160.6 \pm 14.3	141.9 \pm 14.7	136.7 \pm 13.2	134.8 \pm 13.0	134.5 \pm 13.1 *** ###
Mean change (mmHg)		-18.7	-23.9	-25.9	-26.1
95% confidence intervals of mean changes		(-20.0;-17.4)	(-25.3;-22.5)	(-27.2;-24.5)	(-27.5;-24.7)
<i>Captopril+hydrochlorothiazide</i>					
Mean \pm s.d. (mmHg)	160.1 \pm 14.2	145.4 \pm 15.0	141.0 \pm 13.6	138.7 \pm 14.5	138.3 \pm 14.0 ***
Mean change (mmHg)		-14.6	-19.0	-21.4	-21.8
95% confidence intervals of mean changes		(-16.0;-13.3)	(-20.4;-17.6)	(-22.9;-19.9)	(-23.4;-20.2)
<i>DBP</i>					
<i>Delapril+indapamide</i>					
Mean \pm s.d. (mmHg)	101.6 \pm 4.7	89.2 \pm 8.0	85.8 \pm 7.5	84.5 \pm 7.1	84.5 \pm 7.0 ***###
Mean change (mmHg)		-12.4	-15.8	-17.1	-17.1
95% confidence intervals of mean changes		(-13.1;-11.6)	(-16.5;-15.1)	(-17.8;-16.3)	(-17.8;-16.4)
<i>Captopril+hydrochlorothiazide</i>					
Mean \pm s.d. (mmHg)	101.0 \pm 4.8	90.5 \pm 7.8	87.3 \pm 7.2	86.3 \pm 7.4	85.5 \pm 8.0 ***
Mean change (mmHg)		-10.5	-13.8	-14.7	-15.5
95% confidence intervals of mean changes		(-11.3;-9.7)	(-14.5;-13.0)	(-15.5;-13.9)	(-16.3;-14.6)

***= P <0.001 compared with baseline; ### ANCOVA P <0.01 between treatments.

events occurred in patients previously treated with ACE inhibitors. No significant change in the haematology and biochemistry safety test was recorded throughout the study period. The incidence of laboratory values outside the normal range is reported in Table 6.

Discussion

Delapril is an effective and well-tolerated anti-hypertensive drug, which combines particularly well with diuretics like indapamide.¹⁴ The combination of the ACE inhibitor captopril with the diuretic hydrochlorothiazide has been widely used in antihypertensive treatment for several years; therefore, it represents a useful reference therapy

for the evaluation of the effects of newer antihypertensive approaches such as the combination D+I.

In the present study, the efficacy and tolerability of the long-term administration of the combination D+I was assessed in hypertensive patients. The limitations of an open-label study are offset by two important characteristics, that is, the duration of the study (6 months) and the number of patients enrolled (more than 800). In the Abbou study,¹⁵ indapamide was administered for 4 months, and a significant reduction in blood pressure was observed after 6 weeks of treatment. In another study,²² performed in diabetic patients, an evident antihypertensive effect was present after only 4 weeks of therapy. In our study, the D+I combination was able to normalise blood pressure in more than 70% of the patients after 1 month, and in more than 90% after 2 months of treatment. Both C+H and D+I

Table 6 Laboratory values outside the normal range at the end of the 6-month observation period in both groups

	<i>Delapril+indapamide n=396</i>		<i>Captopril+hydrochlorothiazide n=394</i>	
	<i>Baseline</i>	<i>6 months</i>	<i>Baseline</i>	<i>6 months</i>
Na+	1 (0.25%)	2 (0.50%)	0 (0.00%)	2 (0.51%)
K+	1 (0.25%)	3 (0.76%)	0 (0.00%)	1 (0.25%)
Serum glucose	12 (3.02%)	11 (2.77%)	11 (2.78%)	11 (2.78%)
Urea	2 (0.50%)	3 (0.76%)	0 (0.00%)	1 (0.25%)
Creatinine	1 (0.25%)	2 (0.50%)	2 (0.51%)	2 (0.51%)
AST	1 (0.25%)	0 (0%)	4 (1.01%)	0 (0%)
ALT	5 (1.26%)	0 (0%)	5 (1.26%)	0 (0%)
Total cholesterol	54 (13.6%)	42 (10.6%)	34 (8.59%)	26 (6.57%)
LDL cholesterol	24 (6.05%)	22 (5.54%)	22 (5.56%)	20 (5.05%)
HDL cholesterol	13 (3.27%)	3 (0.76%)	8 (2.02%)	2 (0.51%)
Triglycerides	26 (6.55%)	26 (6.55%)	27 (6.82%)	16 (4.04%)

were effective in lowering blood pressure; however, D+I showed a more pronounced effect, both in terms of overall reduction of blood pressure and percentage of responders to therapy. In the present study, D+I significantly reduced not only SBP and DBP but also PP, and this is an important finding because recent studies have shown that a reduction in PP may be prognostically favourable for the hypertensive

patient.^{23–25} This greater efficacy was obtained without any increase in adverse effects, since both treatments were equally well tolerated. Delapril 30 mg +indapamide 1.25 mg produced a greater reduction in blood pressure than that reported in a similar study in which indapamide 1.25 mg was given together with a different ACE inhibitor, perindopril 4 mg/day.¹¹

Another aim of the present study was to investigate the effects of the two treatments on the metabolic profile (lipids, electrolytes, uric acid, etc). Owing to the large number of centres participating in the study, it was impossible to standardise the laboratory results. It was therefore decided to evaluate the number of patients with laboratory values outside the normal limits at the various time points.

It is well known that diuretics may induce hypokaliemia and changes in the lipid pattern (increase in total cholesterol, LDL-cholesterol and triglycerides; decrease in HDL-cholesterol). In the present study both treatments had a neutral impact on circulating cholesterol or triglycerides. Only few patients had laboratory values of sodium, potassium and uric acid outside the normal limits during treatment. The variations recorded during the study were very small, and may well be ascribed to random modification rather than to the effects of the different treatments. However, any interpretation of the results has to be cautious in view of the lack of laboratory standardisation.

A limitation of the study is the lack of a placebo administration during the run-in period. Therefore, the extent of a possible placebo effect cannot be quantified: however, albeit present, it should have equally affected both active treatment.

A second limitation is related to the classification in responders and nonresponders. Albeit widely used, these classifications are, at least in part, arbitrary.

In conclusion, both D+I and C+H have proved to be effective in reducing blood pressure in mild to moderate essential hypertension. The antihypertensive effect of D+I was significantly greater than that of C+H, in terms of reduction in blood pressure and responder rate, while the safety profile of the two treatments was similar.

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Centres that provided the cases

Div. I[^] Medicina Generale Osp. Galliera—Genova; Servizio di Cardiologia Osp. Sacro Cuore—Negrar; U.O. Medicina Interna I Pres. Osp. Della Misericordia—Grosseto; Servizio di Cardiologia Osp. Civile—Policoro; Div. di Cardiologia Osp. Civile—Francavilla Fontana; I Divisione di Medicina Ospedali Riuniti—Foggia; Divisione di Cardiologia Osp. Civile—Carbonia; Azienda Ospedaliera S. Martino—Genova; Serv. Autonomo di Cardiologia Osp. Civile A. Tortora—Pagani; Div. di Dialisi e Nefrologia Osp. S. Raffaele—Milano; Rep. di Medicina e Geriatria Presidio Ospedaliero—Montagnana; Div. di Medicina I Osp. Civile Castello S.G. e Paolo—Venezia; Istituto di Patologia Speciale Medica Osp. Le Scotte—Siena; Div. di Cardiologia Osp. S. Giuseppe da Copertino—Copertino; Serv. Autonomo Cardiologia Presidio Ospedaliero—Polistena; Divisione di Medicina Osp. Civile A.G. Mastino—Bosa; Div. di Medicina Osp. Civile—Asti; Serv. di Cardiologia Osp. Civile—Modica; Div. di Cardiologia Osp. Civile—Partinico; Serv di Cardiologia Osp. Civile S. Salvatore—Pesaro; Div. di Medicina Osp. Gen. Reg.

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