Tables of Treatments in PODCAST trial

The first column is timing in the trial. BP levels are at clinic, and lipid levels are measured ~2 weeks before clinic. The systolic BP and LDL-cholesterol numbers given below are rounded to avoid detailed unblinding. are as beginning of clinic. The drugs are as those as prescribed at end of clinic. The comments come from members of the Trial Steering Committee – Philip Bath, Gary Ford, John Reckless – and are suggestions as to what might be best practice for the trial.

Example of intensive BP therapy reaching target, at least some of the time

Clinic visit	SBP (rounded)	BP drugs at end of clinic	Comments
Baseline, pre-randomisation	140	Lisinopril 5 mg od + Atenolol 25 mg od	
Baseline, post-randomisation		Lisinopril 10 mg od + Atenolol 25 mg od	Treatment escalated appropriately, but note ACE-I and ß-blockers are not very effective together. Suggest follow BHS-NICE A/CD rule, e.g. use lisinopril and amlodipine together
1	130	Lisinopril 10 mg od	Treatment reduced from two to one agents although not at target. A CCB such as amlodipine (or diuretic) could have been added, or the lisinopril titrated up to 20 mg.
2	110	Lisinopril 10 mg od	Treatment left appropriately.
3	140	Lisinopril 10 mg od + Atenolol 50 mg od	Treatment escalated, but not with best drug class – see above
6	120	Lisinopril 10 mg od + Atenolol 50 mg od	Treatment left appropriately
Baseline, pre-randomisation	140	Amlodipine 5 mg od	
Baseline, post-randomisation		Amlodipine 10 mg od	Treatment escalated appropriately
1	?	?	No data?
2	120	Amlodipine 10 mg od	Treatment left appropriately

Examples of intensive BP therapy never reaching target

Clinic visit	SBP (rounded)	BP drugs at end of clinic	Comments
Baseline, pre-randomisation	160	Diltiazem 120 mg od	
Baseline, post-randomisation		Perindopril 2 mg od + Bendro 2.5 mg od	Treatment escalated appropriately
1	140	Perindopril 2 mg od + Diltiazem 120 mg od + Bendro 2.5 mg od	Treatment escalated appropriately. Perindopril dose could also have been increased to 4 mg.
2	160	Diltiazem 120 mg od	Patient confused over what meds they were on. But treatment should have been re-escalated
3	130	Perindopril 2 mg od + Diltiazem 120 mg od	Treatment being re-established
6	145	Perindopril 2 mg od + Diltiazem 120 mg od	Treatment left, but should have been escalated, e.g. increase perindopril to 4 mg od, or add indapamide 2.5 mg od
Baseline, pre-randomisation	? (not measured)	Nil	BP should have been measured
Baseline, post-randomisation		Perindopril 4 mg od	Treatment started, but apparently in ignorance of BP
1	?	Perindopril 4 mg od	BP should have been measured
2	145	Perindopril 8 mg od	Treatment escalated appropriately
3	140	Perindopril 4 mg od + Bendro 2.5 mg od	Treatment changed (reduction of perindopril dose, and addition of bendro); it might have been better to add indapamide (rather than bendro as per NICE) to perindopril 8 mg od
6	140	Perindopril 8 mg od	Treatment reduced by changing back to a regime that was ineffective before
Baseline, pre-randomisation	? (not measured)	?	BP should have been measured
Baseline, post-randomisation		?	
1	160	Perindopril 4 mg od	Treatment escalated appropriately, but NICE BHS would suggest starting with a CCB, e.g. amlodipine 5 mg od
2	175	Perindopril 6 mg od	Treatment escalated, but insufficiently – suggest increase perindopril to 8 mg od, or add amlodipine 5 mg od
Baseline, pre-randomisation	135	Lisinopril 20 mg od + Felodipine 10 mg od + Hydrochlorothiazide ? mg od	
Baseline, post-		Lisinopril 20 mg od +	Treatment escalated with a ß-blocker. But it

randomisation		Bisoprol 2.5 mg od + Felodipine 10 mg od + Hydrochlorothiazide ? mg od	might have been more appropriate to add spironolactone 25 mg od as a fourth line agent unless there was a specific indication for adding a ß-receptor antagonist
1	140	Lisinopril 20 mg od + Bisoprol 5 mg od + Felodipine 10 mg od + Hydrochlorothiazide ? mg od	Treatment escalated appropriately (but see above comment re spironolactone)
2	130	Lisinopril 20 mg od + Bisoprol 5 mg od + Felodipine 10 mg od + Hydrochlorothiazide ? mg od	Treatment left since near, but not at target. We need to get below target. Adding spironolactone 25 mg (or doxazosin) would have been desirable
Baseline, pre-randomisation	185	Perindopril 8 mg od	Note: SBP 186 mmHg is above BP screening criteria. It will be very difficult to achieve target from this level
Baseline, post-randomisation		Bendro 2.5 mg od	Treatment was changed whereas it should have been escalated, i.e. add a diuretic (or better a CCB) to the ACE-I
1	170	Amlodipine 5 mg od	Treatment changed again. It would have been better to add a second/third agent, i.e. ending up on perindopril+ bendro+ amlodipine
Baseline, pre-randomisation	160	Amlodipine 5 mg od	
Baseline, post-randomisation		Amlodipine 10 mg od	Treatment escalated appropriately
1	140	Amlodipine 10 mg od	Treatment left but should have been escalated, e.g. add perindopril 2 mg od
Baseline, pre-randomisation	130	Candesartan 2 mg od	
Baseline, post-randomisation		Candesartan 4 mg od	Treatment escalated appropriately

Example of intensive lipid therapy reaching target, at least some of the time

Clinic visit	LDL-c (rounded)	Lipid drugs at end of clinic	Comments
Baseline, pre-randomisation	2.5	Simvastatin 40 mg on	
Baseline, post-randomisation		Atorvastatin 80 mg od	Treatment escalated appropriately
3	3.0	Atorvastatin 80 mg od + Ezetemibe 10 mg od	Treatment escalated again appropriately
6	2.0	Atorvastatin 80 mg od	Treatment decreased although not yet at target (<2 mmol/l); subject to AEs, dual therapy should have been left on
Baseline, pre-randomisation	1.5	Fluvastatin 40 mg od	
Baseline, post-randomisation		Atorvastatin 80 mg od	Treatment escalated
3	1.5	Atorvastatin 80 mg od	Treatment left appropriately
6	1.5	Atorvastatin 80 mg od	Treatment left appropriately
Baseline, pre-randomisation	1.0	Simvastatin 40 mg on	
Baseline, post-randomisation		Simvastatin 40 mg on	Treatment left appropriately
3	0.5	Simvastatin 40 mg on	Treatment left appropriately
6	0.5	Simvastatin 40 mg on	Treatment left appropriately
Baseline, pre-randomisation	TC=3.5	Simvastatin 20 mg on	
Baseline, post-randomisation		Simvastatin 20 mg on	Treatment left appropriately (since TC < secondary target)
3	?	?	No month 3 visit?
6	2.5	Simvastatin 20 mg bd	Treatment escalated but to simvastatin twice daily. It might have been better to escalate to a more powerful statin, e.g. atorvastatin 80 mg od
Baseline, pre-randomisation	TC=4.5	Simvastatin 40 mg on	
Baseline, post-randomisation		Atorvastatin 80 mg on	Treatment escalated appropriately
3	1.5	Atorvastatin 80 mg on	Treatment left appropriately
6	1.5	Atorvastatin 80 mg on	Treatment left appropriately
Baseline, pre-	1.5	Simvastatin 40	

randomisation		mg on	
Baseline, post-randomisation		Simvastatin 40 mg on	Treatment left appropriately
3	1.5	Simvastatin 40 mg on	Treatment left appropriately
6	1.5	Simvastatin 40 mg on	Treatment left appropriately
Baseline, pre-randomisation	3.0	Atorvastatin 10 mg od	
Baseline, post-randomisation		Atorvastatin 40 mg od	Treatment escalated appropriately, but suggest go straight to maximum dose of atorvastatin 80 mg od. It may be necessary to add ezetimibe 10 mg od at the next visit to help reach target
Baseline, pre-randomisation	1.5	Simvastatin 40 mg on	
Baseline, post-randomisation		Atorvastatin 80 mg od	Treatment escalated
Baseline, pre-randomisation	2.0	Simvastatin 40 mg on	
Baseline, post-randomisation		Simvastatin 80 mg on	Treatment escalated appropriately, but note MHRA do not recommend simvastatin 80 mg in older people; atorvastatin 80 mg od would have been the preferred choice.

Example of intensive lipid therapy NOT reaching target

No examples!!

Comments

Blood pressure lowering (intensive)

- It is vital that BP is measured and recorded at baseline and then at each follow-up clinic visit
- The target is systolic BP <125 mmHg. But equally, it is vital to maximise the difference in SBP between intensive and guideline groups, i.e. at least SBP difference 10 mmHg.
- Follow the 2011 NICE-BHS guidelines where possible. Ideally, start with a 'C-drug' first-line (calcium channel blocker, e.g. amlodipine 5 mg od), then add an 'A-drug' second-line (ACE-I or ARA, e.g. perindopril 2 mg od or losartan 50 mg od), then add a 'D-drug' third-line (thiazide-like diuretic, e.g. indapamide 2.5 mg od), then add a potassium-sparing diuretic (fourth-line, e.g. spironolactone 25 mg od). Avoid ß-receptor antagonists in mono/di/tri-therapy unless there is a specific indication (ß-receptor antagonists may be useful 4th or 5th line).
- Adding a new BP drug at medium dose is usually more effective at lowering BP than increasing the dose of an existing drug.
- For most BP drugs, dose escalation means a doubling of dose, i.e. perindopril 4mg to 8mg, not 6 mg.
- Continue to escalate treatment if the target is not reached, subject to adverse events.
    - SBP =125 mmHg has not reached target (since the target is <125 mmHg) and BP-lowering treatment should be escalated.
- Patients with very high BP at baseline, or needing 4 drugs, should be investigated for secondary causes of hypertension.
- Two changes can be made at a clinic, e.g. add a second agent at the clinic, and increase the dose of an existing drug 2 weeks later. This will allow the target to be achieved faster.
- Do not routinely comment on BP levels or alter treatment in guideline patients. These patients are managed as per routine in the community by their GP. However, if the SBP is very high (≥160 mmHg), as a duty of care, the patient should be asked to visit their GP soon to discuss their BP management; again, no change to their medication should be offered or prescribed.

Lipid lowering (intensive)

- It is vital that fasting lipids are measured and recorded before baseline and before each follow-up clinic visit. Please remember to ask for LDL-c as well as TC/TG. If your lab will no routinely perform a fasting lipid profile, make it clear that the LDL-c is our target measure (or refer samples to an adjacent lab who will provide a LDL-c).
- The target is LDL-c <2 mmol/l. (If the TG are high, then LDL will not be calculated so use the TC target, TC <4 mmol/l.) But equally, it is vital to maximise the difference in LDL-c between intensive and guideline groups, i.e. at least LDL-c difference 1.0 mmHg.
- From May 2012, when atorvastatin goes generic, please start it at baseline, where possible, in patients randomised to intensive lipid-lowering therapy. Atorvastatin may be started at full dose (80 mg) without titration up, as per the SPARCL trial.
- Continue to escalate treatment if the target is not reached, subject to adverse events.
    - LDL-c =2.0 mmol/l has not reached target (since target is <2.0 mmol/l) and lipid-lowering treatment should be escalated; reaching LDL-c of 1.5 mmol/l is quite acceptable (and probably desirable).
- Do not routinely comment on lipid levels or alter treatment in guideline patients. These patients are managed as per routine in the community by their GP. However, if the TC is very high (TC ≥7 mmol/l), as a duty of care, the patient should be asked to visit their GP soon to discuss their lipid management; again, no change to their medication should be offered or prescribed.

General

- In general, reaching target for BP appears to be more challenging than for LDL-cholesterol. It is vital to positively escalate treatment, unless significant adverse events have appeared, at each visit, including adding new drugs and increasing the dose of existing drugs.
- The PODCAST group of patients can get confused easily so explain changes to drug therapy very carefully, ideally writing down what needs to be done.
- Let GPs know what is happening so that they do not over-rule, unnecessarily, treatment changes.

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