Intensive blood pressure control reduces incidence of adverse cardiovascular outcomes (focus on the SPRINT trial)


Clinical Question: Is intensive lowering of blood pressure better than standard management in reducing the incidence of adverse cardiovascular outcomes?

Authors’ conclusion: Intensive lowering of BP (<120 mm Hg) in high risk population reduces the risk of major cardiovascular events.

Background

Treatment of hypertension is critical to the observed reduction in the incidence of its associated complications such as cardiovascular disease, stroke and chronic kidney disease. However, literature shows disagreement with respect to a question in this regard: What is the optimal cut-off for the management of hypertension? A large individual patient data meta-analysis in this area shows a proportional increase in mortality related to vascular mortality for a systolic blood pressure (SBP) > 115 mm Hg[3]. Recommendations of the Eighth Joint National Committee (JNC 8) revised treatment goals for hypertension management based on evidence review[4]. The evidence is strong to support to recommend a target of 150/90 mm Hg for population > 60 years of age; for population <60 years of age the recommended target is 140/90 mm Hg, in spite of insufficient evidence[4]. The number of available studies on a SBP target <140 mm Hg are also limited. Both the studies summarized here [1, 2] attempt to answer this key question– Is intensive lowering of blood pressure better than standard management in reducing the incidence of adverse cardiovascular outcomes?

Objectives

The authors of Systolic Blood Pressure Intervention Trial (SPRINT) group conducted a large prospective randomized control trial (RCT) to investigate the hypothesis that “a lower systolic blood pressure goal (e.g., <120 mm Hg) would reduce clinical events more than a standard goal was designated by a National Heart, Lung, and Blood Institute (NHLBI) expert panel in 2007”[2].

The research group led by Xie et al sought to address this question by conducting a systematic review and meta-analysis in the topic[1].

Methods and Results

The methods and findings of both the studies are presented as a comparative table below (Table 1).

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<tr>
<td>1. Study design</td>
<td>Multi-centric, open-label randomized control trial</td>
<td>Systematic review and Meta-analysis</td>
</tr>
</tbody>
</table>
| 2. Research method | Inclusion criteria for study subjects  
• Above 50 years of age  
• SBP 130 to 180 mm Hg  
• Increased risk of cardiovascular events  
Exclusion criteria  
• Diabetes mellitus  
• Prior history of stroke  
- Study participants were randomly assigned based on treatment target into standard- | Systematic literature search for randomized trials which compared different blood pressure targets with pharmacological interventions for a follow-up period of at least 6 months. From the selected studies, data was extracted from the selected publications and quantitated. |
treatment group (<140 mm Hg) or intensive-treatment group (<120 mm Hg).
- Participants in both arms were maintained on treatment target with anti-hypertensives.
- Follow-up was done monthly for first 3 months followed by a 3 monthly period; total planned follow-up period was 5 years.

3. Study outcomes
Incidence of adverse cardiovascular events, end stage kidney disease, cerebrovascular events, hypotension, syncope, injurious falls, electrolyte abnormalities, bradycardia and death due to any cause.

Results

4. Study Participants
A total of 9361 participants were recruited into the study and assigned into the standard-treatment (N=4678) or intensive-treatment group (N=4683).

A total of 4300 records were identified by literature search from which 21 publications were selected for the study. A total of 44989 participants were included for the quantitative synthesis.

5. Findings
- The incidence of study outcomes were calculated under each of the treatment arms and relative risk (RR) calculated with a 95% confidence interval (CI). P value < 0.05 considered statistically significant.
- A RR of <1 with a significant p value indicates reduced incidence of the particular event in intensive-treatment group.
- A RR of >1 with a significant p value indicates increased incidence of a particular event in intensive-treatment group.

Study outcomes
The results of specific outcomes are shown below. The events with statistical significances are indicated in bold.

| Major cardiovascular event | RR 0.75 (95% CI 0.64–0.89) p<0.001 | RR 0.86 (95% CI 0.78–0.96) p<0.005 |
| Myocardial infarction | RR 0.83 (95% CI 0.64–1.09) p=0.19 | RR 0.87 (95% CI 0.76–1.00) p=0.042 |
| Heart failure | RR 0.62 (95% CI 0.45–0.84) p=0.002 | RR 0.85 (95% CI 0.66–1.11) p=0.24 |
| Death due to cardiac events | RR 0.57 (95% CI 0.38–0.85) p=0.005 | RR 0.91 (95% CI 0.74–1.11) p=0.36 |
| Death due to any cause | RR 0.73 (95% CI 0.60–0.90) p=0.003 | RR 0.91 (95% CI 0.81–1.03) p=0.136 |
| Stroke | RR 0.89 (95% CI 0.63–1.25) p=0.50 | RR 0.78 (95% CI 0.68–0.90) p=0.001 |
| Albuminuria | RR 0.81 (95% CI 0.63–1.04) p=0.10 | RR 0.90 (95% CI 0.84–0.97) p=0.04 |
| GFR decrease (>30%) to <60ml/min/1.73 m² | RR 3.49 (95% CI 2.44–5.10) p<0.001 | NA |

Incidence of adverse events

<table>
<thead>
<tr>
<th>Adverse events</th>
<th>Hazard ratio (HR)</th>
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<tbody>
<tr>
<td>All serious adverse events</td>
<td>HR 1.04 p=0.25</td>
</tr>
<tr>
<td>Hypotension</td>
<td>HR 1.67 p&lt;0.001</td>
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<tr>
<td>Syncope</td>
<td>HR 1.33 p=0.05</td>
</tr>
<tr>
<td>Electrolyte abnormality</td>
<td>HR 1.35 p=0.02</td>
</tr>
<tr>
<td>Injurious fall</td>
<td>HR 0.95 p=0.71</td>
</tr>
<tr>
<td>Acute kidney injury</td>
<td>HR 1.66 p&lt;0.001</td>
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<tr>
<td>Adverse events are represented as RR. The fields where data is not reported are shown as not available (NA).</td>
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Discussion: Results of both studies show evidences in favor of intensive blood pressure control. The participants in intensive-treatment group (<120 mm Hg) had reduced risk of events relating to adverse cardiovascular outcome. Evidences of a lower risk of myocardial infarction, heart failure, mortality, stroke and albuminuria achieved statistical significance in either one of the studies. It is to be noted that the intensive-treatment group had a higher incidence of...
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hypotension episodes, electrolyte abnormalities and acute kidney injury requiring hospitalization. However, the authors of both studies are consistent in their recommendation that intensive blood pressure reduces major cardiovascular events in high risk population, since the benefits outweigh the associated risks.

Another key finding to be noted from the SPRINT study [2] is that participants in the intensive-treatment group (without history of chronic kidney disease at baseline) had a higher risk of glomerular filtration rate (GFR) reduction and acute kidney injury. The progression to CKD was however not significant. Also, the follow-up duration in the study is short (5 years); a longer follow-up would be required to clarify the issue. The authors highlight this point with the caution.

Criticism of the study: The SPRINT trial was not without its share of criticism from physicians across the world. Many felt that the study criteria meant that individuals who were not hypertensive or only mildly hypertensive according to accepted definitions (sBP 132 – 139 mmHg) were being treated thus leading to unnecessary medical treatment of otherwise healthy individuals. The incidence of adverse effects among those with ‘intensive control’ of BP is a matter of concern and cannot be easily dismissed (the study was prematurely stopped because of this). The short follow up of around 2 years in the SPRINT study is a serious shortcoming since it does not clarify whether it reduces the risk of cardiovascular events and renal complications. Many felt that treatment with medications to attain a ‘number’ was given more consideration rather than lifestyle modification especially for those with a systolic BP between 13-139 mmHg. In other words there was a concern that we may end up over-treating those with mild disease. In conclusion, it may be said that the SPRINT study provides some guidelines regarding a target blood pressure for treatment of a hypertensive individual and there is some evidence that tight control reduces the risk of cardiovascular events. However in the light of the potential adverse effects that accompany intensive control of BP and the short follow-up period of the study, it would be wise to restrict this intervention to individuals who have other significant cardiovascular risk factors rather than treat everyone with mild hypertension to achieve the target systolic BP of 120 mmHg.

References

Expert Comments (on the SPRINT trial)
(Dr. Ronald Carey, Assoc. Prof., Department of Medicine, CMC Vellore)

Is the trial valid?
The study seems to have been conducted fairly well with most procedures that are required for a Randomized controlled trial. Even though the study is open label, to conduct a blinded trial in this setting would be tough given that the medications had to be changed based on blood pressure measurements. Some of the drugs have been given by a drug company which could have been avoided. This trial has excluded patients with diabetes and mainly includes patient with mild hypertension already on treatment with a mean baseline BP of 139.7/78.2 in the intensive group and 139.7/78 mm Hg in the standard treatment group. A previous trial done on patients with diabetes with a similar cut off had shown no difference in outcomes. A very significant pitfall in the study is the premature stopping of the trial. This takes away a big chunk of credit away from the study. Having a composite outcome with many components
is also not a generally favored approach. It brings down the number of patients required for the trial but makes the results less reliable.

What are the results?
Keeping the problems with the validity aside, the results provided are statistically significant. With an absolute risk difference of 1.6%, the number needed to prevent the primary outcome (NNT) is 62.5 is a reasonable number for us to apply the results to clinical practice, keeping in mind the increased side effects in the intensive group.

Can I apply the results to my patients?
The BP measurement technique followed in the study (patient sitting quietly for 5 minutes in a separate room) is not how exactly BP is measured in a physician’s clinic. The patients are older, non diabetics, with no history of stroke but nevertheless have a risk for cardiovascular disease. Given the problems in the validity and the side effects and the smaller group of patients for whom the results are applicable, and the fact that a major study (ACCORD) did not find the approach useful in diabetics, it may be prudent for us to wait for more evidence than rush and apply the results to patients in our practice.

Expectant management in preterm pre-mature rupture of membranes: Findings from the PPROMT trial

Summary prepared by: Dr. Anand R, Assistant Professor, Department of Biochemistry, CMC Vellore

Clinical question: Is it better to try immediate delivery or wait (expectant management) in cases of premature rupture of membranes?

Authors’ conclusion: In the absence of maternal or fetal compromise the authors recommend expectant management for preterm PROM.

Background
Guidelines for premature rupture of membranes (PROM) at term (>37 weeks of gestation), recommend immediate delivery based on evidences of reduced incidence of maternal infections without increasing the risks of perinatal morbidity[1]. On the other hand, cases of PROM at extreme preterm (23-30 weeks of gestation) are managed expectantly (in the absence of maternal or fetal indications for immediate delivery) to reduce neonatal complications. However, management guidelines in cases of preterm PROM (between 30-34 weeks) are not clear. The above study by Morris et al is one of the first large scale studies to compare immediate delivery with expectant management in cases of preterm PROM.

Methods
The PPROMT trial was a multi-centric randomized control trial involving 65 centres in 11 countries. Women with a singleton pregnancy and PROM between 34-36 weeks and 6 days of gestation (maternal age>16 years without contraindications to continuing pregnancy) were recruited for the study. Participants were randomly assigned to immediate birth group (n=924) or expectant management group (N=915). Women assigned to immediate birth group had their deliveries < 24h of recruitment. Women in the expectant management group were delivered after onset of labor at term, according to obstetric indications. In both groups, antibiotics deemed best according to local guidelines were given. Incidence of neonatal sepsis was the primary outcome of the study; other neonatal and maternal outcomes were also compared between the groups.
Results
Baseline characteristics of the participants in both arms were similar. Comparison of neonatal outcomes between the groups showed no difference in APGAR score, incidence of neonatal sepsis, pneumonia, circulatory compromise and perinatal or infant mortality. However, there was a significant decrease in the incidence of respiratory distress syndrome, use of mechanical ventilation, decreased hospital/ICU stay in the expectant management group. When the maternal outcomes were compared, mothers in the expectant management group had a marginally higher risk for antepartum/ intrapartum hemorrhage, fever and longer hospital stay. The risks for postpartum hemorrhage and cord prolapse were similar in both groups.

Discussion
In cases of preterm PROM, expectant management is associated with better neonatal outcome without increasing risks of adverse events. There is a marginal trade-off in the risks of maternal outcomes specifically, the incidence of antepartum/intrapartum hemorrhage, fever and prolonged stay in hospital. The result of the primary outcome (risk of neonatal sepsis) of the PPROMT trial is similar to the smaller PPROMEXIL-2 trial in this area[2]. Major strengths of the study include the large sample size and minimal dropout rates of participants.

References

Expert opinion
Dr. Manisha Beck, Associate professor, Department of Obstetrics & Gynaecology, CMC Vellore

Preterm premature rupture of membranes (PPROM) accounts for nearly 40% of all preterm births. While there are clear cut guidelines on how to manage pregnant women with ruptured membranes at term, this is not so in the case of PPROM. Recommendations from American college and Royal College of Obstetricians and Gynecologists, UK (ACOG and RCOG) recommend planned delivery if a pregnant woman presents with leaking per vaginum after 34 weeks.

Expectant management (which means waiting for spontaneous onset of labour) may be associated with complications such as maternal and neonatal sepsis, abruption and cord prolapse. Immediate delivery following PPROM, on the other hand, leads to iatrogenic prematurity and its associated risks like intraventricular haemorrhage, hyaline membrane disease, necrotising enterocolitis etc. The benefits and risks of each approach, therefore, have to be clearly weighed.

The PPROMT trial, is the largest trial till date, which has tried to find out answers for the existing clinical dilemma. Being a multicentric, multicountry trial, the validity of results can be relied upon with confidence. The study design was good and the loss to follow up minimal, which are some of the salient features of a good clinical trial. The results of the trial showed that immediate delivery does not curtail the risk of neonatal and maternal sepsis in comparison to expectant management. Interestingly, the results were similar even in mothers who had Group B streptococcal (GBS) infection, since GBS infection in mother is known to cause early onset neonatal sepsis. Moreover, the risk of respiratory distress was significantly more in the immediate delivery group (p value 0.02). This is likely to be secondary to prematurity.

The only drawback of the trial is that the researchers have excluded twin pregnancies from the study. Hence, we still don’t know whether the findings from the study can be extrapolated to twin pregnancies. Another clinical trial would be needed to find out the optimal management of PPROM in cases of twin pregnancies.

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