National Institute for Health and Care Excellence

Final

Hypertension in adults: diagnosis and management

[I] Evidence review for same-day specialist review

NICE guideline NG136

Prognostic evidence review underpinning recommendations 1.5.1 to 1.5.3 in the guideline

August 2019

Final

This evidence review was developed by the National Guideline Centre

Update information

Minor changes since publication

July 2022: In recommendation 1.5.1 we clarified the options for people with a blood pressure of 180/120 mmHg or more and no target organ damage.

See https://www.nice.org.uk/guidance/ng136 for details

Disclaimer

The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or service users. The recommendations in this guideline are not mandatory and the guideline does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and, where appropriate, their carer or guardian.

Local commissioners and providers have a responsibility to enable the guideline to be applied when individual health professionals and their patients or service users wish to use it. They should do so in the context of local and national priorities for funding and developing services, and in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities. Nothing in this guideline should be interpreted in a way that would be inconsistent with compliance with those duties.

NICE guidelines cover health and care in England. Decisions on how they apply in other UK countries are made by ministers in the Welsh Government, Scottish Government, and Northern Ireland Executive. All NICE guidance is subject to regular review and may be updated or withdrawn.

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1.1 Review question: What factors indicate the need for same-day specialist review (including the possible presence of malignant or accelerated hypertension)?

1.2 Introduction

In most individuals diagnosed with hypertension, their blood pressure has gradually increased over many years resulting in an increased annual risk of future cardiovascular events. Rarely, blood pressure may rise rapidly over hours or days in a condition called malignant or accelerated hypertension. In this condition, there is an immediate risk of serious harm as the blood pressure increases above levels that target organs (that is, the brain, heart and kidneys) can manage. These individuals often require a rapid lowering of blood pressure using intravenous medication and should be managed by a specialist.

Currently, there is little guidance either nationally or internationally to identify that people have, or are at risk of developing, accelerated hypertension. This is particularly relevant in community settings where clinicians may be unsure if a very high blood pressure reading is the result of untreated chronic hypertension or instead represents the early phase of accelerated hypertension.

The importance of identifying factors that necessitate same-day specialist review are 2-fold. Firstly, it should ensure that people at risk of accelerated hypertension receive prompt, specialist review. Secondly, it should reduce referrals for specialist review where accelerated hypertension is unlikely. In this chapter, the evidence for factors that indicate the need for same-day specialist review is evaluated.

1.3 PICO table

For full details, see the review protocol in Appendix A.

Table 1: PICO characteristics of review question

Population	Adults (aged over 18 years) with suspected malignant hypertension

Prognostic variables under consideration	People referred for same-day specialist review based on the following symptoms:
	• Diastolic blood pressure (BP) >120 mmHg, systolic blood pressure of >180 mmHg or mean arterial pressure (MAP) >140 mmHg in isolation or in combination with 1 or more of the following:
	  ○ Grade 3 or 4 hypertensive retinopathy
	  ○ Signs of acute organ damage: kidney, heart, eye or brain (confusion)
	  ○ Visual disturbance
	  ○ Headaches
	  ○ Chest pain
	  ○ Seizures

Confounding factors	• Pre-existing secondary hypertension *Studies will be included but downgraded if they do not adjust for pre-existing secondary hypertension. Studies adjusting for other confounding factors will also be considered for inclusion.*

Outcomes	**Critical** • Mortality • Stroke • Diagnosis of malignant or accelerated hypertension • Hospitalisation • Renal dialysis
Study design	• Cohort studies • Case-control studies in the absence of any other evidence • Systematic reviews of the above

1.4 Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual.[24] Methods specific to this review question are described in the review protocol in appendix A.

Declarations of interest were recorded according to NICE's 2014 conflicts of interest policy.

1.5 Clinical evidence

1.5.1 Included studies

No relevant clinical studies relevant to the review protocol were identified.

See also the study selection flow chart in appendix C.

1.5.2 Excluded studies

See the excluded studies list in appendix E.

1.6 Economic evidence

1.6.1 Included studies

No relevant health economic studies were identified.

1.6.2 Excluded studies

No health economic studies that were relevant to this question were excluded due to assessment of limited applicability or methodological limitations.

See also the health economic study selection flow chart in appendix D.

1.6.3 Resource costs

Broader referral criteria would mean a lower specificity and more false positives would be identified, meaning more referrals to hospital. Whereas, stricter criteria would mean a lower sensitivity and people may be missed who genuinely need urgent treatment, which could lead to mortality.

1.7 Evidence statements

1.7.1 Clinical evidence statements

No relevant published evidence was identified.

1.7.2 Health economic evidence statements

No relevant economic evaluations were identified.

1.8 The committee's discussion of the evidence

1.8.1 Interpreting the evidence

1.8.1.1 The outcomes that matter most

The committee considered mortality, stroke, diagnosis of accelerated hypertension, hospitalisation and renal dialysis to be critical outcomes for decision-making. However, no available evidence was identified for any of these outcomes.

1.8.1.2 The quality of the evidence

No studies relevant to the review protocol were identified.

1.8.1.3 Benefits and harms

Although some observational studies were identified in the literature search, they were not applicable to the review question and so no evidence was identified for this review.

The committee discussed consensus recommendations for this topic based on its clinical expertise. The committee discussed the difficulty in differentiating between those that have accelerated hypertension and those that have severe primary hypertension. It discussed the balance of sensitivity and specificity in identifying everyone that has accelerated hypertension and agreed that a broader referral criteria would result in a large number of inappropriate referrals, which would be associated with a large resource impact but could identify more people with accelerated hypertension. More specific referral criteria may be more likely to identify only those who have accelerated hypertension with the risk of missing some people who could be at serious risks of target organ damage and death, as it was noted that untreated accelerated hypertension has around a 95% mortality rate within 1 year. Taking all the above into account, the committee agreed to retain the previous recommendations with some amendments to clarify the symptoms that healthcare professionals should look for. The committee agreed that important symptoms should be added to the recommendation including the presence of emergency features such as chest pain or confusion, to ensure those who appear well but actually have accelerated hypertension are identified. The committee agreed that terms used in the previous recommendations such as headache were nonspecific and the amendment to the recommendation should help to clarify further and specify symptoms to be aware of, resulting in the successful identification of people with accelerated hypertension. The committee noted that healthcare professionals often already ask about the emergency symptoms listed.

The committee agreed it was important for 'new onset' symptoms to be recognised as many of the symptoms listed could pre-exist unrelated to accelerated hypertension, particularly in older people. The recognition of 'new onset' ensures a focus on new symptoms that have rapidly developed and so meeting the specification for accelerated hypertension.

The committee noted the importance of considering retinal problems as a part of the diagnostic criteria for accelerated hypertension. The committee agreed that a specialist referral might be required to identify these symptoms although looking into people's eyes is also a part of identifying target organ damage, as recommended in the current guideline.

It was discussed that there was a need to have a recommendation regarding action for those who had raised blood pressure but none of the listed symptoms. The committee agreed that in this group of people, it was appropriate to recommend an expedited investigation for target organ damage, and only if present, giving treatment. The previous recommendation advised giving treatment based on severe blood pressure alone; however, the committee considered this could result in some people being treated unnecessarily for example, those with stiff arteries or who are anxious or sick, resulting in temporarily raised blood pressure. Related to this, the committee added a new recommendation to repeat blood pressure measurement within 7 days if there is severe raised blood pressure with no adverse features or target organ damage, ensuring these people would be followed up. This would further ensure this population are accurately managed and started on treatment pathways as appropriate.

1.8.2 Cost effectiveness and resource use

No economic evidence was identified for this question.

Accelerated hypertension is a very serious condition with a high risk of mortality if untreated. It is, however, very rare.

No clinical evidence was identified to inform a recommendation, so the committee discussed the advantages and disadvantages of being stricter in their criteria of factors that indicate same day referral. Broader referral criteria would mean a lower specificity and more false positives would be identified meaning more referrals to hospital whereas a stricter criteria would mean a lower sensitivity and people may be missed who genuinely need urgent treatment.

Accelerated hypertension is generally diagnosed by an individual having severe hypertension and changes due to blood pressure damage in the eyes. The decision to admit someone into hospital is based on the presence of emergency features that would lead a clinician to suspect organ damage to be imminent. An individual would also generally be admitted if they had signs of emergency symptoms even without signs of accelerated hypertension. People with severe hypertension but without emergency symptoms or signs of accelerated hypertension would usually not be admitted but would be given antihypertensive treatment.

The committee decided to add to the existing recommendation by listing some emergency features. This would help clinicians with deciding when people should be referred to hospital. Although this may increase referrals, if emergency symptoms are present then these individuals need urgent admission to hospital and using emergency criteria is more likely to ensure that those individuals who were being missed are now not being missed.

Additionally, it was discussed how those with severe hypertension but without signs that would require referral to hospital shouldn't always be started on antihypertensive treatment immediately, as there may be reasons as to why their blood pressure was very high on a particular day, such as anxiety or stress, and does not always mean they have severe hypertension. The recommendation was amended to make clear that investigation for target organ damage should be expedited. Only if there are signs of target organ damage should treatment be started. Additionally, a new recommendation was made to measure blood pressure again within 7 days if the person has severe hypertension but does not have signs to indicate referral or target organ damage.

The committee considered that expediting investigations for target organ damage was feasible. They agreed that these would be investigations that would need to be undertaken anyway, and would involve limited resources. There is also likely to be a saving from not

immediately giving everyone with severe hypertension treatment anymore, which might outweigh the cost of the target organ damage tests being expedited as not everyone would then go onto treatment based on the results. Measuring blood pressure again within 7 days using ambulatory measurement may not be feasible in all parts of the country; however, it should be in the majority of places. As this is the measurement method recommended for diagnosis of hypertension, then this method should be available.

Overall, a small population is likely to be affected by any resource use stated in the recommendation; therefore, these recommendations are not likely to have a resource impact. The added criteria for referral is likely to be a cost effective use of resources because of the consequences of not treating people who have those symptoms, and this will ensure those who need urgent treatment will receive it.

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Appendices

Appendix A: Review protocols

Table 2: Review protocol: Malignant hypertension

Field	Content
Review question	What factors indicate the need for same-day specialist review (including the possible presence of malignant or accelerated hypertension)?
Type of review question	Prognostic review A review of health economic evidence related to the same review question was conducted in parallel with this review. For details, see the health economic review protocol for this NICE guideline.
Objective of the review	To evaluate which factors suggest that a same-day specialist care referral is required, including people with suspected malignant hypertension.
Eligibility criteria – population / disease / condition / issue / domain	Population: Adults (over 18 years) with suspected malignant hypertension
Eligibility criteria – intervention(s) / exposure(s) / prognostic factor(s)	People referred for same day specialist review based on the following symptoms: • Diastolic BP >120 mmHg, systolic blood pressure of >180 mmHg or MAP >140mmHg in isolation or in combination with 1 or more of the following: ○ Grade 3 or 4 hypertensive retinopathy ○ Signs of acute organ damage: kidney, heart, eye or brain (confusion) ○ Visual disturbance ○ Headaches ○ Chest pain ○ Seizures
Eligibility criteria – comparator(s) / control or reference (gold) standard	Confounding factors: • Pre-existing secondary hypertension Studies will be included but downgraded if they do not adjust for pre-existing secondary hypertension. Studies adjusting for other confounding factors will also be considered for inclusion.
Outcomes and prioritisation	**Critical** • Mortality • Stroke • Diagnosis of malignant or accelerated hypertension • Hospitalisation • Renal dialysis
Eligibility criteria – study design	Cohort studies Case-control studies in the absence of any other evidence Systematic reviews of the above
Other inclusion exclusion criteria	Exclusions: • Univariate analysis • People on renal replacement therapy (RRT) • Pregnant women

	• Children and young people (aged under 18 years)
Proposed sensitivity / subgroup analysis, or meta-regression	If possible, subgroup analysis for heterogeneity will be conducted based on the following subgroups: • Age (<55, 55-75, >75)* • Family origin (African and Caribbean, White, South Asian) *To note that we will also extract evidence in those aged 80 years or more if this evidence is reported separately.
Selection process – duplicate screening / selection / analysis	A senior research fellow will undertake quality assurance prior to completion.
Data management (software)	Pairwise meta-analyses will be performed where possible using Cochrane Review Manager (RevMan5). GRADEpro will be used to assess the quality of evidence for each outcome. Endnote will be used for bibliography, citations, sifting and reference management.
Information sources – databases and dates	Medline, Embase, the Cochrane Library Language: Restrict to English only
Identify if an update	Yes, 2011
Author contacts	https://www.nice.org.uk/guidance/cg127
Highlight if amendment to previous protocol	For details, please see section 4.5 of Developing NICE guidelines: the manual.
Search strategy – for 1 database	For details, please see appendix B
Data collection process – forms / duplicate	A standardised evidence table format will be used, and published. There were no relevant studies.
Data items – define all variables to be collected	For details, please see the evidence statements.
Methods for assessing bias at outcome / study level	Standard study checklists were used to appraise individual studies critically. For details, please see section 6.2 of Developing NICE guidelines: the manual The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/
Criteria for quantitative synthesis	For details, please see the methods report for this guideline, and section 6.4 of Developing NICE guidelines: the manual.
Methods for quantitative analysis – combining studies and exploring (in)consistency	For details, please see the separate Methods report for this guideline.
Meta-bias assessment – publication bias, selective reporting bias	For details, please see section 6.2 of Developing NICE guidelines: the manual.
Confidence in cumulative evidence	For details, please see the methods report for this guideline, and section 6.4 of Developing NICE guidelines: the manual.
Rationale / context – what is known	For details, please see the introduction to the evidence review.
Describe contributions of authors and guarantor	A multidisciplinary committee developed the evidence review. The committee was convened by the National Guideline Centre (NGC) and chaired by Anthony Wierzbicki in line with section 3 of Developing NICE guidelines: the manual.

	Staff from the NGC undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate, and drafted the evidence review in collaboration with the committee. For details, please see Developing NICE guidelines: the manual.
Sources of funding / support	The NGC is funded by NICE and hosted by the Royal College of Physicians.
Name of sponsor	The NGC is funded by NICE and hosted by the Royal College of Physicians.
Roles of sponsor	NICE funds the NGC to develop guidelines for those working in the NHS, public health and social care in England.
PROSPERO registration number	Not registered

Table 3: Health economic review protocol

Review question	**All questions – health economic evidence**
Objectives	To identify health economic studies relevant to any of the review questions.
Search criteria	• Populations, interventions and comparators must be as specified in the clinical review protocol above. • Studies must be of a relevant health economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis, comparative cost analysis). • Studies must not be a letter, editorial or commentary, or a review of health economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.) • Unpublished reports will not be considered unless submitted as part of a call for evidence. • Studies must be in English.
Search strategy	A health economic study search will be undertaken using population-specific terms and a health economic study filter – see appendix B below. No date cut-off from the previous guideline was used.
Review strategy	Studies not meeting any of the search criteria above will be excluded. Studies published before 2002, abstract-only studies and studies from non-OECD countries or the US will also be excluded. Studies published after 2002 that were included in the previous guideline(s) will be reassessed for inclusion and may be included or selectively excluded based on their relevance to the questions covered in this update and whether more applicable evidence is also identified. Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in appendix H of Developing NICE guidelines: the manual (2014).[24] **Inclusion and exclusion criteria** • If a study is rated as both 'Directly applicable' and with 'Minor limitations', then it will be included in the guideline. A health economic evidence table will be completed and it will be included in the health economic evidence profile. • If a study is rated as either 'Not applicable' or with 'Very serious limitations', then it will usually be excluded from the guideline. If it is excluded then a health economic evidence table will not be completed and it will not be included in the health economic evidence profile. • If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both, then there is discretion over whether it should be included.

Where there is discretion

The health economist will make a decision based on the relative applicability and quality of the available evidence for that question in discussion with the guideline committee if required. The ultimate aim is to include health economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the committee if required, may decide to include only the most applicable studies and to exclude selectively the remaining studies. All studies excluded based on applicability or methodological limitations will be listed with explanation in the excluded health economic studies appendix below.

The health economist will be guided by the following hierarchies.

Setting:

- UK NHS (most applicable).
- OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden).
- OECD countries with predominantly private health insurance systems (for example, Switzerland).
- Studies set in non-OECD countries or in the US will be excluded before being assessed for applicability and methodological limitations.

Health economic study type:

- Cost–utility analysis (most applicable).
- Other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequences analysis).
- Comparative cost analysis.
- Non-comparative cost analyses including cost-of-illness studies will be excluded before being assessed for applicability and methodological limitations.

Year of analysis:

- The more recent the study, the more applicable it will be.
- Studies published in 2002 or later (including any such studies included in the previous guideline[s]) but that depend on unit costs and resource data entirely or predominantly before 2002 will be rated as ‘Not applicable’.
- Studies published before 2002 (including any such studies included in the previous guideline[s]) will be excluded before being assessed for applicability and methodological limitations.

Quality and relevance of effectiveness data used in the health economic analysis:

- The more closely the clinical effectiveness data used in the health economic analysis match with the outcomes of the studies included in the clinical review, the more useful the analysis will be for decision-making in the guideline.
- Generally, economic evaluations based on excludes from the clinical review will be excluded.

Appendix B: Literature search strategies

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual 2014, updated 2017

For more detailed information, please see the Methodology Review.

B.1 Clinical search literature search strategy

Searches were constructed using 1 or more of the following approaches:

- Population AND Prognostic terms AND Study filter(s)

Table 4: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline (OVID)	1946–02 October 2018	Exclusions Randomised controlled trials Systematic review studies Observational studies Diagnostic tests studies Prognostic studies
Embase (OVID)	1974–02 October 2018	Exclusions Randomised controlled trials Systematic review studies Observational studies Diagnostic tests studies Prognostic studies
The Cochrane Library (Wiley)	Cochrane Reviews to Issue 8 of 12, August 2018 CENTRAL to Issue 7 of 12, July 2018 DARE and NHSEED to Issue 2 of 4, April 2015 HTA to Issue 4 of 4, October 2016	None

Table 5: Medline (Ovid) search terms

1.	Hypertension, Malignant/
2.	((malignant or accelerat* or severe or emergenc* or cris?s or urgenc*) adj3 hypertens*).ti,ab.
3.	((uncontrol* or acute* or rising or risen or raised or excess* or severe or emergen* or cris?s or urgen*) adj3 (blood pressure or BP or hypertens* or arterial pressure)).ti,ab.
4.	or/1-3
5.	exp pregnancy/
6.	exp Hypertension, Pregnancy-Induced/ not exp Hypertension/
7.	(pre eclampsia or pre-eclampsia or preeclampsia).ti,ab.
8.	exp Hypertension, Portal/ not exp Hypertension/
9.	exp Hypertension, Pulmonary/ not exp Hypertension/
10.	exp Intracranial Hypertension/ not exp Hypertension/
11.	exp Ocular Hypertension/ not exp Hypertension/

12.	exp Diabetes Mellitus, Type 1/ not exp Diabetes Mellitus, Type 2/
13.	or/5-12
14.	4 not 13
15.	letter/
16.	editorial/
17.	news/
18.	exp historical article/
19.	Anecdotes as Topic/
20.	comment/
21.	case report/
22.	(letter or comment*).ti.
23.	or/15-22
24.	randomized controlled trial/ or random*.ti,ab.
25.	23 not 24
26.	animals/ not humans/
27.	exp Animals, Laboratory/
28.	exp Animal Experimentation/
29.	exp Models, Animal/
30.	exp Rodentia/
31.	(rat or rats or mouse or mice).ti.
32.	or/25-31
33.	14 not 32
34.	(exp child/ or exp pediatrics/ or exp infant/) not (exp adolescent/ or exp adult/ or exp middle age/ or exp aged/)
35.	33 not 34
36.	limit 35 to English language
37.	randomized controlled trial.pt.
38.	controlled clinical trial.pt.
39.	randomi#ed.ti,ab.
40.	placebo.ab.
41.	randomly.ti,ab.
42.	Clinical Trials as topic.sh.
43.	trial.ti.
44.	or/37-43
45.	Meta-Analysis/
46.	exp Meta-Analysis as Topic/
47.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
48.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
49.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
50.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
51.	(search* adj4 literature).ab.
52.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
53.	cochrane.jw.
54.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
55.	or/45-54

56.	Epidemiologic studies/
57.	Observational study/
58.	exp Cohort studies/
59.	(cohort adj (study or studies or analys* or data)).ti,ab.
60.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
61.	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort* or data)).ti,ab.
62.	Controlled Before-After Studies/
63.	Historically Controlled Study/
64.	Interrupted Time Series Analysis/
65.	(before adj2 after adj2 (study or studies or data)).ti,ab.
66.	or/56-65
67.	exp case control study/
68.	case control*.ti,ab.
69.	or/67-68
70.	66 or 69
71.	Cross-sectional studies/
72.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
73.	or/71-72
74.	66 or 73
75.	66 or 69 or 73
76.	36 and (44 or 55 or 75)
77.	exp "signs and symptoms"/
78.	symptom assessment/
79.	diagnosis/ or prognosis/
80.	(clinical adj3 (manifestation? or feature? or finding? or aspect? or marker?)).ti,ab.
81.	(presenting adj3 (feature? or finding? or factor?)).ti,ab.
82.	presentation?.ti,ab.
83.	(physical adj3 (manifestation? or characteristic? or feature? or finding?)).ti,ab.
84.	(sign or signs or symptom* or recogni* or identif* or complain*).ti,ab.
85.	(diagnos* or prognos* or assess* or criteria* or predict*).ti,ab.
86.	or/77-85
87.	exp "sensitivity and specificity"/
88.	(sensitivity or specificity).ti,ab.
89.	((pre test or pretest or post test) adj probability).ti,ab.
90.	(predictive value* or PPV or NPV).ti,ab.
91.	likelihood ratio*.ti,ab.
92.	likelihood function/
93.	((area under adj4 curve) or AUC).ti,ab.
94.	(receive* operat* characteristic* or receive* operat* curve* or ROC curve*).ti,ab.
95.	(diagnos* adj3 (performance* or accurac* or utilit* or value* or efficien* or effectiveness)).ti,ab.
96.	gold standard.ab.
97.	or/87-96
98.	prognosis/
99.	(predict* or prognos*).ti,ab.
100.	Logistic models/

101.	Disease progression/
102.	or/98-101
103.	exp Survival analysis/
104.	exp Mortality/
105.	or/102-104
106.	36 and (86 or 97 or 105)
107.	76 or 106

Table 6: Embase (Ovid) search terms

1.	*malignant hypertension/
2.	((malignant or accelerat* or severe or emergenc* or cris?s or urgenc*) adj3 hypertens*).ti,ab.
3.	((uncontrol* or acute* or rising or risen or raised or excess* or severe or emergen* or cris?s or urgen*) adj3 (blood pressure or BP or hypertens* or arterial pressure)).ti,ab.
4.	or/1-3
5.	exp pregnancy/
6.	exp maternal hypertension/
7.	(pre eclampsia or pre-eclampsia or preeclampsia).ti,ab.
8.	exp portal hypertension/ not exp hypertension/
9.	exp pulmonary hypertension/ not exp hypertension/
10.	exp intracranial hypertension/
11.	exp intraocular hypertension/ not exp hypertension/
12.	exp insulin dependent diabetes mellitus/ not exp non insulin dependent diabetes mellitus/
13.	or/5-12
14.	4 not 13
15.	letter.pt. or letter/
16.	note.pt.
17.	editorial.pt.
18.	case report/ or case study/
19.	(letter or comment*).ti.
20.	or/15-19
21.	randomized controlled trial/ or random*.ti,ab.
22.	20 not 21
23.	animal/ not human/
24.	nonhuman/
25.	exp Animal Experiment/
26.	exp Experimental Animal/
27.	animal model/
28.	exp Rodent/
29.	(rat or rats or mouse or mice).ti.
30.	or/22-29
31.	14 not 30
32.	(exp child/ or exp pediatrics/) not (exp adult/ or exp adolescent/)
33.	31 not 32
34.	limit 33 to English language
35.	random*.ti,ab.
36.	factorial*.ti,ab.

37.	(crossover* or cross over*).ti,ab.
38.	((doubl* or singl*) adj blind*).ti,ab.
39.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
40.	crossover procedure/
41.	single blind procedure/
42.	randomized controlled trial/
43.	double blind procedure/
44.	or/35-43
45.	systematic review/
46.	meta-analysis/
47.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
48.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
49.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
50.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
51.	(search* adj4 literature).ab.
52.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
53.	cochrane.jw.
54.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
55.	or/45-54
56.	Clinical study/
57.	Observational study/
58.	family study/
59.	longitudinal study/
60.	retrospective study/
61.	prospective study/
62.	cohort analysis/
63.	follow-up/
64.	cohort*.ti,ab.
65.	63 and 64
66.	(cohort adj (study or studies or analys* or data)).ti,ab.
67.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
68.	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort* or data)).ti,ab.
69.	(before adj2 after adj2 (study or studies or data)).ti,ab.
70.	or/56-62,65-69
71.	exp case control study/
72.	case control*.ti,ab.
73.	or/71-72
74.	70 or 73
75.	cross-sectional study/
76.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
77.	or/75-76
78.	70 or 77
79.	70 or 73 or 77

80.	34 and (44 or 55 or 79)
81.	symptom assessment/
82.	diagnosis/
83.	prognosis/
84.	(clinical adj3 (manifestation? or feature? or finding? or aspect? or marker?)).ti,ab.
85.	(presenting adj3 (feature? or finding? or factor?)).ti,ab.
86.	presentation?.ti,ab.
87.	(physical adj3 (manifestaion? or characteristic? or feature? or finding?)).ti,ab.
88.	(sign or signs or symptom* or recogni* or identif* or complain*).ti,ab.
89.	(diagnos* or prognos* or assess* or criteria* or predict*).ti,ab.
90.	exp symptomatology/
91.	or/81-90
92.	exp "sensitivity and specificity"/
93.	(sensitivity or specificity).ti,ab.
94.	((pre test or pretest or post test) adj probability).ti,ab.
95.	(predictive value* or PPV or NPV).ti,ab.
96.	likelihood ratio*.ti,ab.
97.	((area under adj4 curve) or AUC).ti,ab.
98.	(receive* operat* characteristic* or receive* operat* curve* or ROC curve*).ti,ab.
99.	(diagnos* adj3 (performance* or accurac* or utilit* or value* or efficien* or effectiveness)).ti,ab.
100.	diagnostic accuracy/
101.	diagnostic test accuracy study/
102.	gold standard.ab.
103.	or/92-102
104.	exp prognosis/
105.	prognostic assessment/
106.	(predict* or prognos*).ti,ab.
107.	disease course/
108.	statistical model/
109.	or/104-108
110.	exp Survival analysis/
111.	exp Mortality/
112.	or/109-111
113.	34 and (91 or 103 or 112)
114.	80 or 113

Table 7: Cochrane Library (Wiley) search terms

#1.	MeSH descriptor: [Hypertension, Malignant] explode all trees
#2.	((malignant or accelerat* or severe or emergenc* or cris?s or urgenc*) near/3 hypertens*):ti,ab
#3.	((uncontrol* or acute* or rising or risen or raised or excess* or severe or emergen* or cris?s or urgen*) near/3 (blood pressure or BP or hypertens* or arterial pressure)):ti,ab
#4.	(or #1-#3)
#5.	MeSH descriptor: [Signs and Symptoms] explode all trees
#6.	MeSH descriptor: [Symptom Assessment] this term only
#7.	MeSH descriptor: [Diagnosis] this term only
#8.	MeSH descriptor: [Prognosis] this term only

#9.	(clinical near/3 (manifestation* or feature* or finding* or aspect* or marker*)):ti,ab
#10.	(presenting near/3 (feature* or finding* or factor*)):ti,ab
#11.	presentation*:ti,ab
#12.	(physical near/3 (manifestation* or characteristic* or feature* or finding*)):ti,ab
#13.	(sign or signs or symptom* or recogni* or identif* or complain*):ti,ab
#14.	(diagnos* or prognos* or assess* or criteria* or predict*):ti,ab
#15.	(or #5-#14)
#16.	#4 and #15

B.2 Health Economics literature search strategy

Health economic evidence was identified by conducting a broad search relating to hypertension in adults population in NHS Economic Evaluation Database (NHS EED – this ceased to be updated after March 2015) and the Health Technology Assessment database (HTA) with no date restrictions. NHS EED and HTA databases are hosted by the Centre for Research and Dissemination (CRD). Additional searches were run on Medline and Embase for health economics, economic modelling and quality of life studies.

Table 8: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline	2014–28 August 2018	Exclusions Health economics studies
Embase	2014–28 August 2018	Exclusions Health economics studies
Centre for Research and Dissemination (CRD)	HTA - Inception–28 August 2018 NHS EED - Inception to March 2015	None

Table 9: Medline (Ovid) search terms

1.	exp Hypertension/
2.	hypertens*.ti,ab.
3.	(elevat* adj2 blood adj pressur*).ti,ab.
4.	(high adj blood adj pressur*).ti,ab.
5.	(increase* adj2 blood pressur*).ti,ab.
6.	((systolic or diastolic or arterial) adj2 pressur*).ti,ab.
7.	or/1-6
8.	letter/
9.	editorial/
10.	news/
11.	exp historical article/
12.	Anecdotes as Topic/
13.	comment/
14.	case report/
15.	(letter or comment*).ti.
16.	or/8-15
17.	randomized controlled trial/ or random*.ti,ab.
18.	16 not 17

19.	animals/ not humans/
20.	exp Animals, Laboratory/
21.	exp Animal Experimentation/
22.	exp Models, Animal/
23.	exp Rodentia/
24.	(rat or rats or mouse or mice).ti.
25.	or/18-24
26.	7 not 25
27.	limit 26 to English language
28.	Economics/
29.	Value of life/
30.	exp "Costs and Cost Analysis"/
31.	exp Economics, Hospital/
32.	exp Economics, Medical/
33.	Economics, Nursing/
34.	Economics, Pharmaceutical/
35.	exp "Fees and Charges"/
36.	exp Budgets/
37.	budget*.ti,ab.
38.	cost*.ti.
39.	(economic* or pharmaco?economic*).ti.
40.	(price* or pricing*).ti,ab.
41.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
42.	(financ* or fee or fees).ti,ab.
43.	(value adj2 (money or monetary)).ti,ab.
44.	or/28-43
45.	27 and 44

Table 10: Embase (Ovid) search terms

1.	exp Hypertension/
2.	hypertens*.ti,ab.
3.	(elevat* adj2 blood adj pressur*).ti,ab.
4.	(high adj blood adj pressur*).ti,ab.
5.	(increase* adj2 blood pressur*).ti,ab.
6.	((systolic or diastolic or arterial) adj2 pressur*).ti,ab.
7.	or/1-6
8.	letter.pt. or letter/
9.	note.pt.
10.	editorial.pt.
11.	case report/ or case study/
12.	(letter or comment*).ti.
13.	or/8-12
14.	randomized controlled trial/ or random*.ti,ab.
15.	13 not 14
16.	animal/ not human/

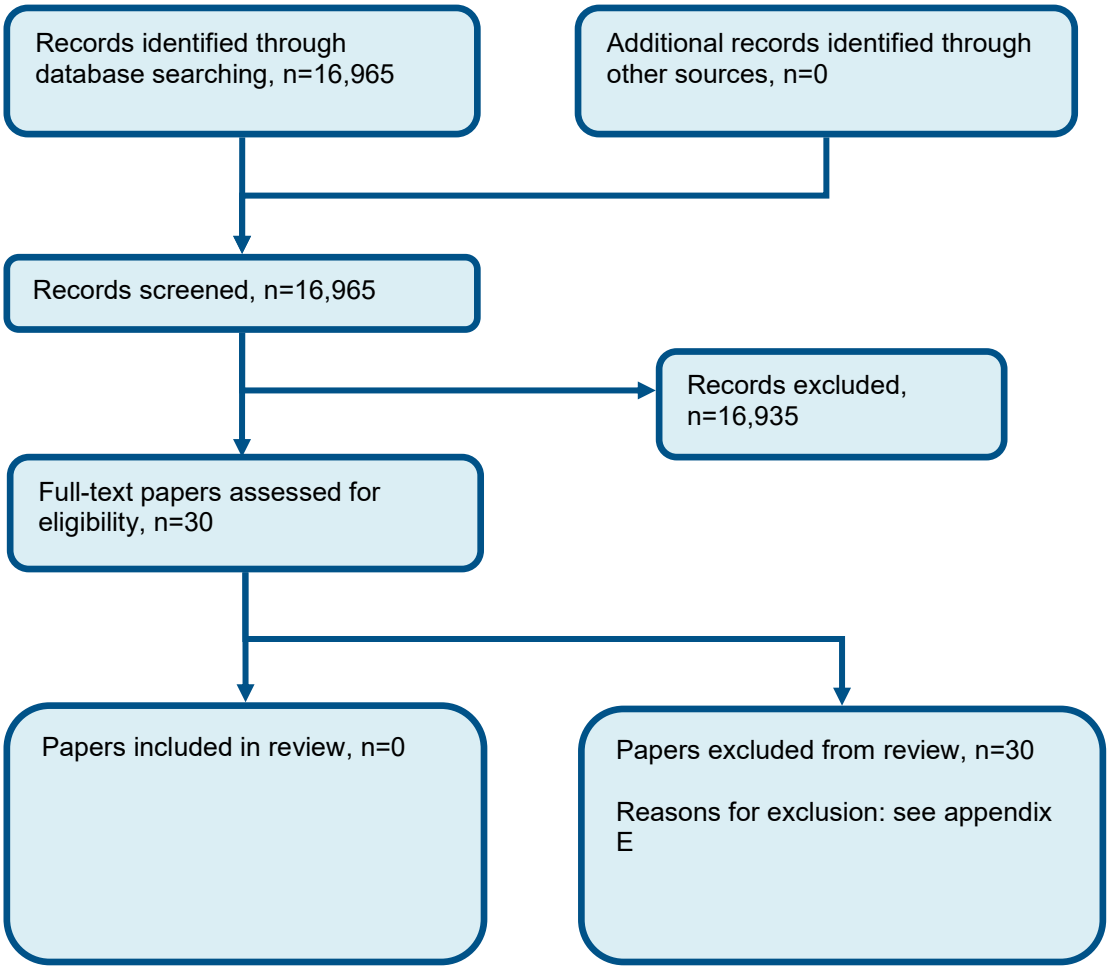
17.	nonhuman/
18.	exp Animal Experiment/
19.	exp Experimental Animal/
20.	animal model/
21.	exp Rodent/
22.	(rat or rats or mouse or mice).ti.
23.	or/15-22
24.	7 not 23
25.	limit 24 to English language
26.	health economics/
27.	exp economic evaluation/
28.	exp health care cost/
29.	exp fee/
30.	budget/
31.	funding/
32.	budget*.ti,ab.
33.	cost*.ti.
34.	(economic* or pharmaco?economic*).ti.
35.	(price* or pricing*).ti,ab.
36.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
37.	(financ* or fee or fees).ti,ab.
38.	(value adj2 (money or monetary)).ti,ab.
39.	or/26-38
40.	25 and 39

Table 11: NHS EED and HTA (CRD) search terms

#1.	MeSH DESCRIPTOR Hypertension EXPLODE ALL TREES IN NHSEED,HTA
#2.	(Hypertens*) IN NHSEED, HTA
#3.	(elevat* adj2 blood adj pressur*) IN NHSEED, HTA
#4.	(high adj blood adj pressur*) IN NHSEED, HTA
#5.	(increase* adj2 blood pressur*) IN NHSEED, HTA
#6.	((systolic or diastolic or arterial) adj2 pressur*) IN NHSEED, HTA
#7.	#1 OR #2 OR #3 OR #4 OR #5 OR #6

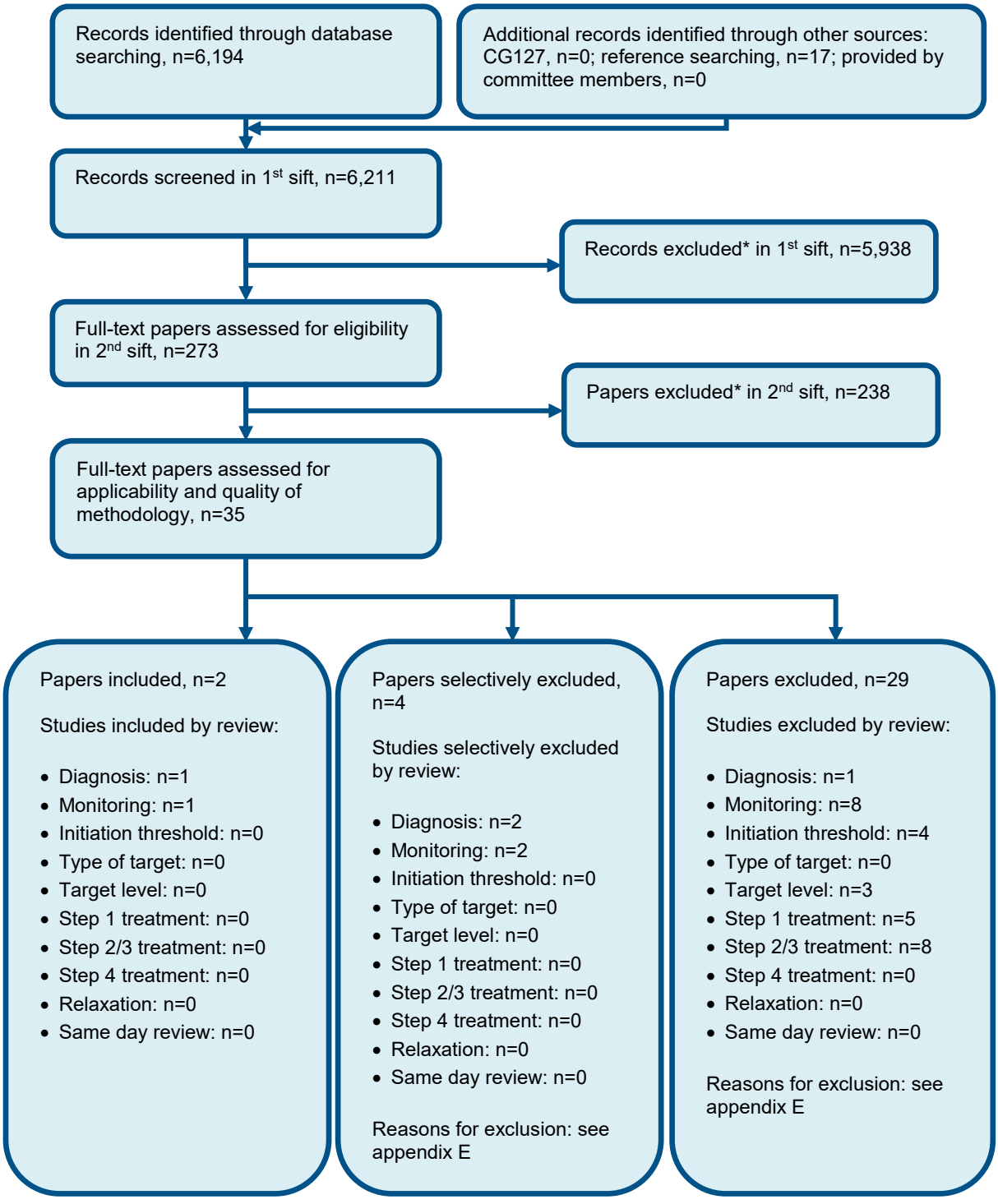
Appendix C: Clinical evidence selection

Figure 1: Flow chart of clinical study selection for the review of malignant hypertension



Appendix D: Health economic evidence selection

Figure 2: Flow chart of health economic study selection for the guideline



* Non-relevant population, intervention, comparison, design or setting; non-English language

Appendix E: Excluded studies

E.1 Excluded clinical studies

Table 12: Studies excluded from the clinical review

Reference	Reason for exclusion
Amraoui 2014[1]	Population does not match protocol
Anonymous 1960[2]	Incorrect study design (editorial)
Anonymous 1991[3]	Incorrect study design (correction on previously published paper)
Bahemuka 1985[4]	Population does not match protocol
Bennett 1979[5]	Incorrect study design, population does not match protocol
Bulpitt 1985[6]	Population does not match protocol
Cummings 1974[7]	Population does not match protocol
Curry 1975[8]	Incorrect study design, population does not match protocol
Dranov 1974[9]	Incorrect study design
Guiga 2017[10]	Multivariate analysis not used
Januszewicz 2016[11]	Incorrect study design, population does not match protocol
Lane 2009[12]	Population does not match protocol
Lee 2018[13]	Population does not match protocol
Lima 2005[14]	Population does not match protocol
Lip 1995[15]	Population does not match protocol
Lip 2000[16]	Population does not match protocol
Lip 1994[17]	Population does not match protocol
Mamdani 1974[18]	Population does not match protocol
Martin 2004[19]	Multivariate analysis not used
Milne 1989[20]	Population does not match protocol
Misra 2002[21]	Incorrect intervention, incorrect study design (describing current recognition and management of hypertension)
Monteiro Junior 2008[22]	Population does not match protocol
Nakamoto1999[23]	Population does not match protocol
Paini 2018[25]	Multivariate analysis not used
Patel 1990[26]	Population does not match protocol
Perloff 1994[27]	Population does not match protocol
Ram 1990[28]	Incorrect study design, population does not match protocol
Talks 1996[29]	Population does not match protocol
van den Born 2006[30]	Multivariate analysis not used
Wiebe 2014[31]	Population does not match protocol

E.2 Excluded health economic studies

None.

Appendix F: Research recommendations

F.1 Same-day hospital specialist assessment

Research question: Which people with extreme hypertension (220/120 mmHg or higher) or emergency symptoms should be referred for same-day hospital specialist assessment?

Why this is important:

More than a million people in the UK have sub-optimally controlled hypertension. A small minority will have features suggesting imminent life-threatening or life-changing target organ damage, including those with extreme hypertension with symptoms progressing quickly. While same-day referral for specialist assessment in hospital can be lifesaving, it is costly, and most people without emergency features or accelerated disease are unlikely to benefit sufficiently from such acute services over and above elective treatment.

Criteria for selecting high-priority research recommendations:

PICO question	Population: People with hypertension and either emergency features or signs of accelerated hypertension Prognostic variable: emergency features or signs of accelerated hypertension Outcome(s): Same day referral to hospital medical services and patient important outcomes of all-cause mortality and cardiovascular events including myocardial infarction, stroke and health-related quality of life.
Importance to patients or the population	Many people with uncontrolled hypertension could be referred to the hospital urgently with substantial cost and distress to them, yet only a minority are likely to benefit. People, GPs and hospital doctors need to know who benefits.
Relevance to NICE guidance	High quality research in this area may enable future updates of this guidance to make a strong recommendation on the referral criteria of people with urgent features or accelerated hypertension to hospital medical services.
Relevance to the NHS	Identifying the minority of people with sub-optimally controlled hypertension with emergency features or accelerated phase disease who would benefit from same-day referral is of substantial interest to affected people and NHS acute services.
National priorities	Streamlining appropriate same-day hospital referrals is essential to meet urgent waiting time targets such as the 4-hour wait and ensure cost effective use of limited NHS resources.
Current evidence base	A systematic review of the current evidence of the accelerated phase of hypertension was undertaken. No evidence was identified capturing those without accelerated hypertension who have emergency features of impending life threatening or life changing target organ damage. A strong recommendation could not be made based on the available evidence.
Equality	None.
Study design	Cohort study assessing those currently referred for same-day assessment with uncontrolled hypertension or urgent features compared to people with similar levels of uncontrolled hypertension without emergency or accelerated features. Multivariate analysis should be included adjusting for possible confounding factors.
Feasibility	Collaboration of multiple acute hospitals is likely to be needed to address this question in a timely fashion.
Other comments	None.

Importance	High: the research is essential to inform future updates of key recommendations in the guideline. The need to make best use of limited acute NHS medical services is pressing.