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The NoLoCo Strategy for Essential Hypertension

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Ninety-nine percent of all "essential" hypertension can be controlled by using the NoLoCo strategy, without causing any significant side-effects and without an increase in insulin resistance. NoLoCo stands for Norvasc (amlodipine), Lozol (indapamide), and Cozaar (losartan), but the medicines are considered and used in reverse order.

Cozaar (losartan) is the initial medication used because it treats hypertension closest to the source of the problem in the rennin-angiotensin system. ARBs are preferable to ACE inhibitors because they have less side-effects while having similar efficacy. Cozaar is an ARB of the highest efficacy, but has a unique benefit of being the only ARB that will also lower the uric acid level, and elevated uric acid levels have been associated with increased risk of cardiovascular disease in some studies. The usual starting dose of Cozaar is 50 mg. but about 50% of patients will eventually need to be increased to 100 mg.

Lozol (indapamide) is the next medication that should be considered for use after Cozaar because thiazide diuretics work synergistically with ARBs (and with ACE inhibitors) to lower blood pressure. This synergism occurs because both ARBs and ACE inhibitors work best in high renin environments, and the thiazide diuretics work very well to produce a high renin state in patients. Lozol is a second generation thiazide diuretic, and as such does not cause many of the thiazide side-effects to the same extent that the first generation thiazide diuretics (such as hydrochlorothiazide and chlorthalidone) do. These side-effects include hypercholesterolemia, hypertriglyceridemia, hyperglycemia, and hyperuricemia. Also, while hypertrophic cardiomyopathy will still progressively develop in patients whose blood pressure is well controlled with hydrochlorothiazide, this is not the case with indapamide. The reduced side-effect profile of indapamide as compared to first generation thiazide diuretics is most likely because indapamide does not contribute significantly to insulin resistance, while first generation thiazide diuretics are known to. A dose of 2.5 mg. of indapamide is equivalent to a dose of 25 mg. of hydrochlorothiazide, but many patients may only require 1.25 mg. to achieve the desired effect when used synergistically with and ARB or ACE inhibitor. Potassium supplementation should usually be started at the same time that indapamide is started because hypokalemia is associated with increased blood pressure, however, in patients with known renal insufficiency potassium supplementation should be delayed until the potassium level and renal function can be assessed after a week or two on indapamide.

Norvasc (amlodipine) is the next antihypertensive to be considered in this strategy because of its great efficacy and relatively low incidence of side-effects when compared to other dihydropyridine calcium channel blockers. Its vasodilatory effects greatly complement those of Cozaar, and it is one of the few dihydropyridine calcium channel blockers that do not have a negative inotropic effect at therapeutic doses. Norvasc is the dihydropyridine calcium channel blocker that is least likely to cause lower extremity edema, and when used in the NoLoCo strategy the development of edema with amlodipine is very rare, probably because of the concomitant use of a diuretic. The usual starting dose of amlodipine is 5 mg., but in more severe hypertension 10 mg. can be considered, and in the very frail and elderly 2.5 mg. might be considered.

Losartan and indapamide take about a week to begin to work after they have been started, and a very significant effect can be obtained after two weeks of therapy, which is probably the

best time to bring the patient back for a recheck of blood pressure and blood chemistries. The full effects of these medications are not achieved for up to two months. By contrast, amlodipine begins to significantly lower blood pressure within 24 hours, and the full effect of a regular dose of amlodipine can usually be achieved within three to five days. Patients should usually be rechecked two weeks after a medication change to evaluate blood pressure, and also to recheck blood chemistries. In cases of severe hypertension in which all three medications of the strategy are started at the same time, consideration should be given to bringing the patient back for a recheck after only one week on the medications.

Consideration may be given to substituting a different ARB for Cozaar, and Diovan (valsartan) seems to have comparable efficacy to Cozaar, however, Cozaar is the only ARB that lowers uric acid. Consideration may also be given to substituting an ACE inhibitor for the ARB, and the best ACE inhibitor to use for such a purpose is lisinopril, however, the ACE inhibitors seem to have more side-effects than the ARBs, and it is important to remember not to start a potassium supplement at the same time as indapamide and an ACE inhibitor because of the potassium sparing effects of the ACE inhibitor. While amlodipine is the most efficacious dihydropyridine calcium channel blocker and also has the lowest incidence of side-effects in that class, substitution of nifedipine or nicardipine in their extended release forms might be considered.

When using this strategy an effort should be made to minimize other medications that tend to increase insulin resistance, such as NSAIDs. Maximal therapy in the NoLoCo strategy should be considered to be 100 mg. of Cozaar (losartan), 2.5 mg. of Lozol (indapamide), and 10 mg. of Norvasc (amlodipine). Remember that potassium supplementation should usually be started at the same time as indapamide (but not when starting an ACE inhibitor at the same time), and the best choice for such supplementation is Micro-K 10 Meq after food once daily, and all of these medicines are best given in the morning after breakfast. In the rare cases in which hypertension cannot be adequately controlled solely by using the No-Lo-Co strategy, clonidine should be considered as an efficacious adjunct.